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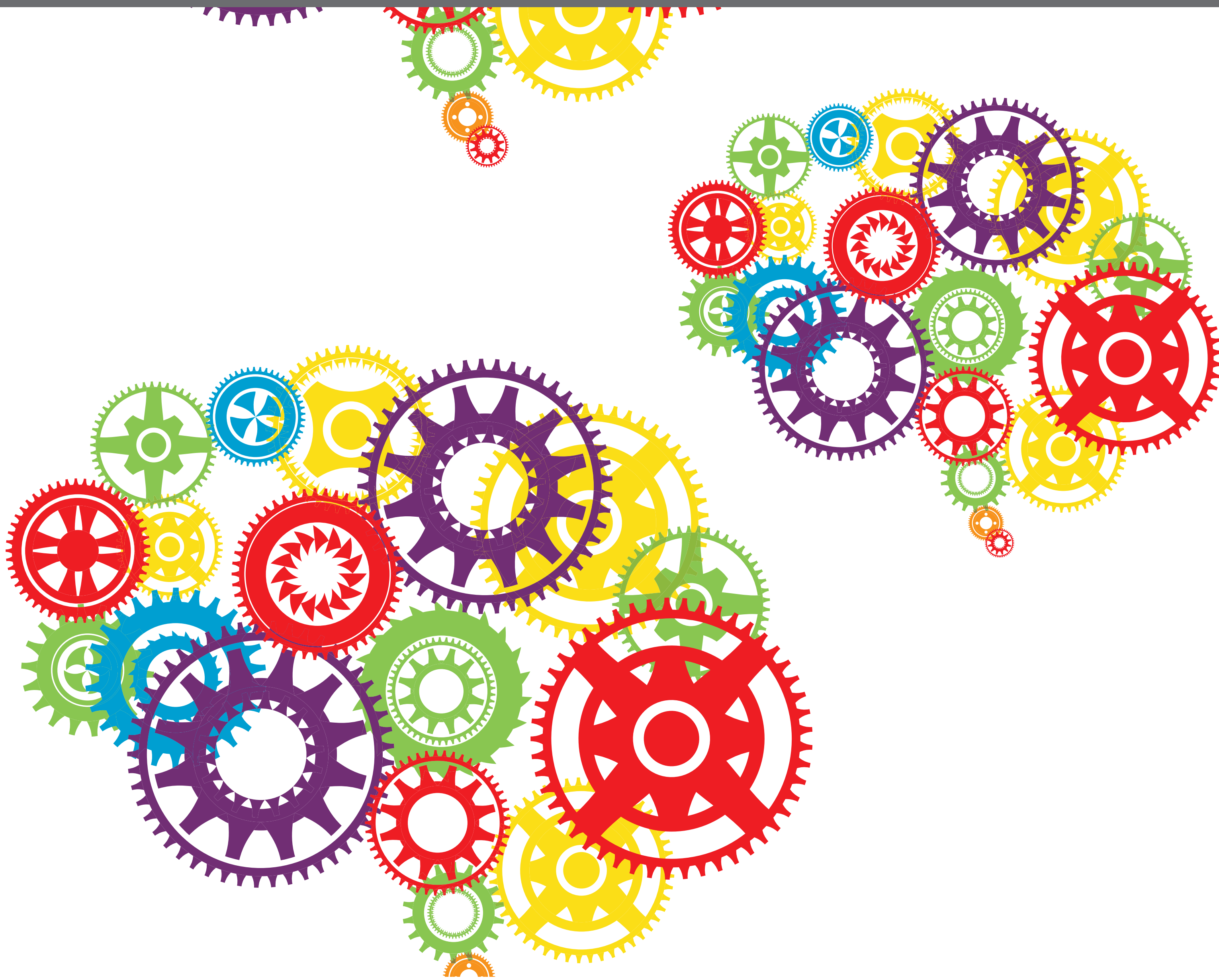

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SENSORY NEUROSCIENCE EDITOR'S PICK 2021

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Self Beyond the Body: Action-Driven and Task-Relevant Purely Distal Cues Modulate Performance and Body Ownership

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Our understanding of body ownership largely relies on the so-called Rubber Hand Illusion (RHI). In this paradigm, synchronous stroking of the real and the rubber hands leads to an illusion of ownership of the rubber hand provided that it is physically, anatomically, and spatially plausible. Self-attribution of an artificial hand also occurs during visuomotor synchrony. In particular, participants experience ownership over a virtual or a rubber hand when the visual feedback of self-initiated movements follows the trajectory of the instantiated motor commands, such as in the Virtual Hand Illusion (VHI) or the moving Rubber Hand Illusion (mRHI). Evidence yields that both when the cues are triggered externally (RHI) and when they result from voluntary actions (VHI and mRHI), the experience of ownership is established through bottom-up integration and top-down prediction of proximodistal cues (visuotactile or visuomotor) within the peripersonal space. It seems, however, that depending on whether the sensory signals are externally (RHI) or self-generated (VHI and mRHI), the top-down expectation signals are qualitatively different. On the one hand, in the RHI the sensory correlations are modulated by top-down influences which constitute empirically induced priors related to the internal (generative) model of the body. On the other hand, in the VHI and mRHI body ownership is actively shaped by processes which allow for continuous comparison between the expected and the actual sensory consequences of the actions. Ample research demonstrates that the differential processing of the predicted and the reafferent information is addressed by the central nervous system via an internal (forward) model or corollary discharge. Indeed, results from the VHI and mRHI suggest that, in action-contexts, the mechanism underlying body ownership could be similar to the forward model. Crucially, forward models integrate across all self-generated sensory signals including not only proximodistal (i.e., visuotactile or visuomotor) but also purely distal sensory cues (i.e., visuoauditory). Thus, if body ownership results from a consistency of a forward model, it will be affected by the (in)congruency of purely distal cues provided that they inform about action-consequences and are relevant to a goal-oriented task.

Specifically, they constitute a corrective error signal. Here, we explicitly addressed this question. To test our hypothesis, we devised an embodied virtual reality-based motor task where action outcomes were signaled by distinct auditory cues. By manipulating the cues with respect to their spatial, temporal and semantic congruency, we show that purely distal (visuoauditory) feedback which violates predictions about action outcomes compromises both performance and body ownership. These results demonstrate, for the first time, that body ownership is influenced by not only externally and self-generated cues which pertain to the body within the peripersonal space but also those arising outside of the body. Hence, during goal-oriented tasks body ownership may result from the consistency of forward models.

Keywords: body ownership, internal forward models, multisensory integration, top-down prediction, goal-oriented behavior, task-relevant cues

1. INTRODUCTION

Humans and other species simultaneously acquire and integrate both self-generated (i.e., reafferent) and externally-generated (i.e., exafferent) information through different sensory channels (Sperry, 1950). Hence, the ability of the nervous system to generate unambiguous interpretations about the body, the so-called body ownership, and determine the source and relevance of a given sensation is fundamental in adaptive goal-oriented behavior (Botvinick and Cohen, 1998; Wolpert and Flanagan, 2001; Van Den Bos and Jeannerod, 2002; Ehrsson, 2012). Imagine playing Air Hockey where the objective is to score points by hitting a puck into the goal. To accomplish the task, at every trial, the brain prepares and generates actions which are most likely to elicit the desired trajectory leading the puck toward the target (Wolpert and Flanagan, 2001; Sober and Sabes, 2003; Shadmehr et al., 2010). Simultaneously, it predicts the sensory consequences of those actions from proprioceptive or tactile modalities which inform about the position and location of the arm, and from visual or auditory modalities which inform about the position and location of the puck (Miall and Wolpert, 1996; Ernst and Bülthoff, 2004; Makin et al., 2008). Since both types of cues may constitute a corrective error signal for the consecutive trial, they are both relevant to the task (Shadmehr et al., 2010; Wolpert et al., 2011). This evidence suggests that the internal models of the external environment, the motor apparatus, and the body are being continuously shaped and updated through sensorimotor interactions of an agent with the world (Miall and Wolpert, 1996; Tsakiris, 2010; Blanke, 2012; Apps and Tsakiris, 2014). Specifically, this tuning occurs through a combination, integration, and prediction of both reafferent and exafferent signals from multisensory sources (Prinz, 1997; Ernst and Bülthoff, 2004; Noë, 2004). However, mechanisms driving the representation of self and, in particular, body ownership in action contexts which require manipulation of the environment and therefore integration of not only proximal or proximodistal but also purely distal cues remain elusive.

In fact, our understanding of body ownership largely relies on the so-called Rubber Hand Illusion (RHI) where subjects passively receive sensory stimuli (Botvinick and Cohen, 1998). RHI is a well-established paradigm (Botvinick and Cohen, 1998; Makin et al., 2008; Tsakiris, 2010) where the illusion of ownership toward a rubber hand emerges during externally-generated synchronous, but not asynchronous, stroking of the real and fake hands (Botvinick and Cohen, 1998). The illusion generalizes to distinct body-parts including fingers, face or a full body (Lenggenhager et al., 2007; Dieguez et al., 2009; Sforza et al., 2010). Initially, Botvinick and Cohen (1998) proposed that the illusion of ownership over the rubber hand is a rather passive sensory state which emerges reactively from a bottom-up integration of multisensory, in this case, visuotactile signals (i.e., proximodistal). Interestingly, subsequent studies investigating mechanisms underlying the RHI extended this classical interpretation by demonstrating that the intermodal matching is not sufficient for the experience of ownership (Tsakiris, 2010). In particular, it has been revealed that the RHI strictly requires physical, anatomical, postural and spatial plausibility of the real and fake hands (Tsakiris and Haggard, 2005; Costantini and Haggard, 2007; Lloyd, 2007; Makin et al., 2008) (see also Liepelt et al., 2017). Hence, the bottom-up integration of multisensory inputs seems to be modulated by experience-driven predictive information, which allows for active comparison between the properties of the viewed (non)-corporeal object and the internal model of the body (Tsakiris et al., 2008; Apps and Tsakiris, 2014). The finding of Ferri et al. (2013, 2017) further supported the fundamental role of the top-down processes in the modulation of body ownership. The authors demonstrated that the experience of ownership over a non-bodily object could originate as a consequence of pure expectation and anticipation of correlated exafference in the absence of actual tactile stimulation (Ferri et al., 2013, 2017). Together, this evidence supports the hypothesis that in the context of externally generated inputs (classical RHI), body ownership relies on two intertwined processes. Namely, (1) the bottom-up accumulation and integration of tactile and visual cues, and (2) top-down comparison between the novel sensory stimuli (i.e., rubber hand) and experience-driven priors about the internal model of the body (Tsakiris and Haggard, 2005; Blanke, 2012; Clark, 2013; Seth, 2013; Apps and Tsakiris, 2014). We will refer to tactile or proprioceptive modalities as *proximal*, requiring an object to enter in direct contact with the surface of the body, and to the visual or auditory modalities as *distal*, sensing from a distance without getting in direct contact with the body.

Only recently the principles of body ownership have been studied in the context of self-generated (reafferent) sensory signals using physical set-ups (i.e., moving Rubber Hand Illusion, mRHI) (Tsakiris et al., 2006; Dummer et al., 2009; Kammers et al., 2009; Newport et al., 2010; Walsh et al., 2011; Ma and Hommel, 2015a,b), or virtual reality (i.e., moving Virtual Hand Illusion, VHI) (Sanchez-Vives et al., 2010; Kalckert and Ehrsson, 2012; Shibuya et al., 2018). In these protocols which include movement (mRHI and VHI), subjects are typically instructed to reach a specific target (goal-oriented) or to move the fingers/hand/arm continuously within a specific area (free exploration) while observing the (a)synchronously moving rubber or virtual analog. The results yield that there is a strong experience of ownership in the condition where the movements of the real and fake arms are spatiotemporally aligned (Dummer et al., 2009). Contrarily, participants report no ownership of the fake body-part when the visual feedback of self-initiated movement is (inconsistently) delayed or displaced, and therefore does match the proprioceptive information (Blakemore et al., 2000). Hence, similar to the classical RHI, in the context of self-generated movements, ownership seems to depend on the consistency of sensory information from proximodistal modalities, in this case, proprioceptive (proximal) and visual (distal). Interestingly, different to the classical RHI, in VHI as well as mRHI the experience of ownership emerges independently of whether (1) the visual, anatomical or structural properties of the avatar satisfy well-established priors about the own body (Banakou et al., 2013; Peck et al., 2013; Ma and Hommel, 2015a; Romano et al., 2015; Van Dam and Stephens, 2018), (2) there is a (consistent) delay in the visual feedback of the movement (3) the viewed object is 'connected' to participants' body (Ma and Hommel, 2015a). Crucially, the condition which needs to be satisfied is that the action-driven sensory feedback from proximodistal modalities matches the predicted one (Dummer et al., 2009; Sanchez-Vives et al., 2010; Ma and Hommel, 2015b). In line with physiological and motor control studies (Miall and Wolpert, 1996; Wolpert and Flanagan, 2001; Proske and Gandevia, 2012), this evidence suggests that when moving in a goal-oriented manner body ownership is weighted stronger by the congruency of the internal (forward) model of the action and the action effects, the same mechanism which impacts agency (Gallagher, 2007; Hommel, 2009; Longo and Haggard, 2009; D'Angelo et al., 2018), rather than the (generative) model of the body and its physical specifics Ma and Hommel (2015b). Crucially, it has been well established that the forward models are not limited to the bodily (proximal or proximodistal) feedback exclusively, but instead, they integrate across all sensory predictions which pertain to the interactions of an agent within an environment, including purely distal cues (Jordan and Rumelhart, 1992; Miall and Wolpert, 1996). For instance, under normal conditions, the visuoauditory signals of the puck hitting the goal are spatiotemporally aligned with its trajectory that depends on the direction of the arm movement. However, if the actual location of the sound of the puck hitting the goal does not correspond to the efference copy or corollary discharge, it would reflect on the Sensory Prediction Errors (SPE) of the forward model (Wolpert et al., 1995, 2011; Miall and Wolpert, 1996; Woodgate et al., 2015; Maffei et al., 2017). Thus, if body ownership results from a consistency of forward models, it would be affected by the (in)congruency of not only proximodistal cues such as in the mRHI and VHI (Dummer et al., 2009; Sanchez-Vives et al., 2010) but also purely distal signals given that they constitute task-relevant information about the action-consequences.

Here, we propose that in contexts where the sensory signals are self-generated, such as in the moving Rubber Hand Illusion or the Virtual Hand Illusion, body ownership depends on the sensory prediction errors from purely distal multisensory modalities, which would suggest a mechanism similar to the forward model or corollary discharge. We, therefore, hypothesize that the experience of ownership over a virtual body will be compromised when action-driven and task-relevant visuoauditory feedback of goal-oriented movements will not match sensory predictions. We also expect that the incongruency of those cues will affect performance. To test this hypothesis, we devise an embodied virtual reality-based goal-oriented task where action outcomes are signaled by distinct auditory signals. We manipulate the cues with respect to their spatial, temporal and semantic congruency, and compare body ownership and performance across two experimental conditions, where purely distal cues are either congruent or incongruent. Our results demonstrate, for the first time, that purely distal signals which violate predictions about the consequences of action-driven outcomes affect both performance and body ownership.

2. MATERIALS AND METHODS

2.1. Participants

After providing written informed consent, sixteen healthy participants were recruited for the study, eight males (mean age 24.0 ± 2.65) and eight females (mean age 22.64 ± 2.25). Since no previous study assessed the effects of the congruency of purely distal modalities on body ownership, we could not perform a power analysis to determine the sample size. We, therefore, based the choice of N on previous studies (Mohler et al., 2010). All subjects were right-handed (handedness assessed using the Edinburgh Handedness Inventory) (Oldfield, 1971), had normal or corrected-to-normal vision and reported normal hearing. They were pseudorandomly assigned to two experimental groups following a between-subjects design, which prevented habituation to the ownership measures, visuoauditory manipulations, and fatigue. We used stratified randomization to balance the conditions in terms of age, gender and previous experience with virtual reality. All participants were blind to the purpose of the study. The experimental procedures were previously approved by the ethical committee of the University of Pompeu Fabra (Barcelona, Spain).

2.2. Task: Virtual Reality-Based Air Hockey.

The experimental setup (**Figure 1A**) comprised a personal computer, a motion detection system (Kinect, Microsoft,

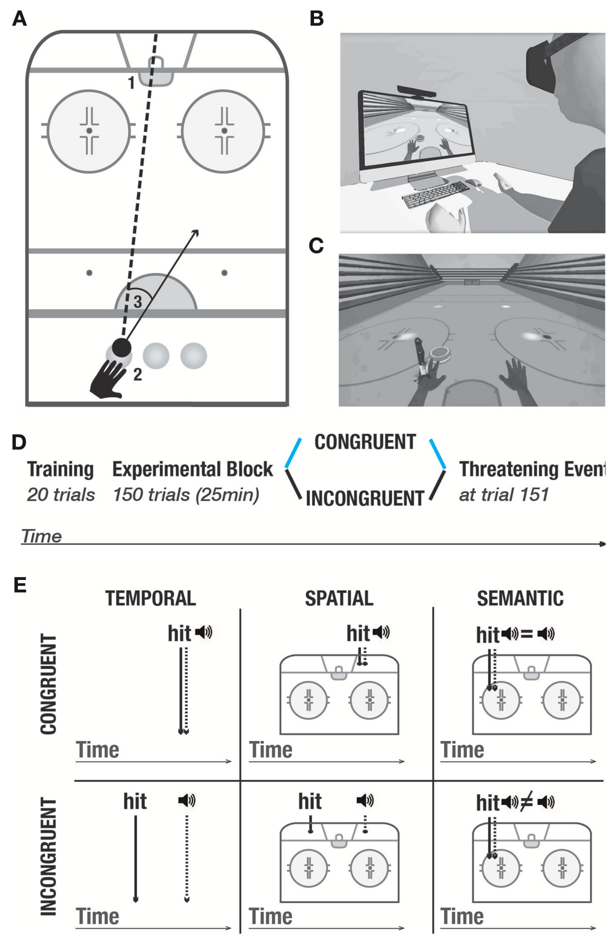

FIGURE 1 | Experimental setup and protocol. **(A)** Task. 1- goal. 2- three starting positions. 3- example of a directional error, calculated as the difference between the actual direction vector and a straight line between the position of the puck and the goal. **(B)** Experimental setup. **(C)** Threatening event. **(D)** Experimental protocol. All participants underwent the training block. In the experimental block, they were randomly split into two conditions: Congruent (blue), and incongruent (black). At trial 151, all participants went through the threatening event which served to measure galvanic skin responses. The same color-code (congruent- blue, incongruent- black) is used in the following figures. **(E)** Purely distal visuoauditory manipulations- temporal, spatial and semantic. Upper panel: congruent condition; lower panel: incongruent condition.

Seattle), a Head Mounted Display (HTC Vive, www.vive.com) and headphones.

Similar to others (Sanchez-Vives et al., 2010; Grechuta et al., 2017), here we used virtual reality as a tool to study the modulation of body ownership. The protocol was integrated within the virtual environment of the Rehabilitation Gaming System (Cameirão et al., 2010; Grechuta et al., 2014). During the experiment, while seated at a table, participants were required to complete a goal-oriented task that consisted in hitting a virtual puck into the goal (air hockey, **Figure 1A**, B1). The virtual body was spatially aligned to the real body. Throughout the experiment, the participants' arm movements were continuously tracked and mapped onto the avatar's arms, such that the subjects interacted with the virtual environment by making planar, horizontal movements over a tabletop (**Figures 1A, B**). To prevent repetitive gestures, at the beginning of every trial the puck pseudorandomly appeared in one of the three starting positions (left, center, right) (**Figure 1** B2). The frequency of appearance of every starting position was uniformly distributed within every experimental session. Participants received instructions to place their hand in an indicated starting position and to execute the movement to hit the puck when its color changed to green ("go" signal). Each trial consisted of one "hit" which could end in either a success (the puck enters the goal) or a failure (the puck hits one of the three walls). At the end of every trial, participants were to place their left hand back at the starting position. The experimental block, in both conditions, consisted of 150 trials preceded by 20 trials of training (training block) (**Figure 1D**) and followed by a threatening event. The threatening event served to measure autonomous responses to an unexpected threat (body ownership measure, **Figure 1C**) (Armel and Ramachandran, 2003). Overall, the task had an approximate duration of 20 min.

2.3. Multisensory Feedback.

Task-Relevant Visuomotor Signals. Throughout the experiment, participants were exposed to the visual feedback of self-generated arm movements. Specifically, the real arms were tracked by the motion detection input device and mapped onto the avatar's arms in real time allowing synchronous feedback. This method served to control for the congruency of proximodistal (i.e., visuomotor) signals which has been shown to underlie body ownership and agency (Sanchez-Vives et al., 2010). It also guaranteed that the only manipulated variables were the distal modalities (i.e., visual and auditory).

Task-Relevant Visuoauditory Signals. The task included task-relevant distal cues in the form of auditory feedback which was triggered as a consequence of every interaction of the puck with the environment. In particular, at the end of every trial, an auditory cue constituted a binary reinforcement signal informing about a failure (negative sound) or a success (positive sound). To study whether purely distal cues influence body ownership and performance, we manipulated the congruency of the auditory stimuli in three domains (**Figure 1E**) — temporal: the time of the cue was synchronized with the time of the hit; spatial: the cue originated from the location of the hit, and semantic: the feedback of the cue reflected performance in a binary way (i.e., success or failure). The auditory cues were manipulated in two experimental conditions including congruent and incongruent. In the training block and the congruent condition, auditory cues were always congruent such that they occurred at the time of the hit, at the location of the hit, and they reflected performance. In the incongruent condition, the auditory signals were always incongruent. Namely, (1) the sound of the hit was anticipated or delayed, that is, it occurred randomly within 200–500 ms before or after the actual collision (temporal domain), (2) it originated in a different location than the actual hit, that is, 5–15° away from the actual hit, or (3) it did not reflect performance, that is participants heard the sound of failure following a successful trial and vice versa (semantic domain).

We chose those three manipulations to include all the dimensions necessary for the performance of the present task: direction, force, as well as the knowledge of results. Each of the dimensions (spatial, temporal, and semantic) provides unique information to the subject about the consequences of one's actions. Specifically, (1) the spatial dimension informs about the direction of the ballistic movement (where the puck hits the wall/goal), (2) the temporal dimension informs about the force applied to the action (when the puck reaches the wall/goal), whereas (3) the semantic dimension informs about the outcome of the action (either success or a failure). As such, all these dimensions contribute to the generation of prediction errors that can be integrated by an internal model to adjust motor performance. Spatial and temporal dimensions provide information about the action parameters on a continuous range and can be used as a supervising signal whereas the semantic dimension constitutes a binary reinforcement signal. All manipulations were pseudorandomly distributed and counterbalanced within each session to counteract order effects. Importantly, task-relevant proximodistal cues such as the visual feedback of the arm movements remained congruent in both conditions.

2.4. Measures

2.4.1. Motor Control

We used three measures to quantify performance: scores, directional error, and reaction times. Scores were calculated as the percentage of successful trials (the puck enters the gate), while the directional error indicated the absolute angular deviation from the straight line between the starting position of the puck (left, central or right) and the center of the gate (**Figure 1**, B3). We computed the reaction times as time intervals between the appearance of the puck and action initiation. Since the task did not impose a time limit, we expected neither significant differences in reaction times between the conditions nor speed-accuracy trade-offs. We predicted that the manipulations of purely distal (visuoauditory) action-driven signals in the incongruent condition might alter scores and directional accuracy as compared to the congruent condition.

2.4.2. Body Ownership

Galvanic Skin Response (GSR). At the end of every experimental session, in both conditions, we introduced a threatening event (a knife falling to stab the palm of the virtual hand, **Figure 1C**) to quantify autonomous, physiological responses to an unexpected threat (Armel and Ramachandran, 2003). To prevent movement-driven muscular artifacts, we recorded the skin conductance responses from the right hand which did not move during the experiment. For the analysis, we calculated the mean and the standard deviation of the integral of the baseline (10 s time window before the threatening stimulus onset)-subtracted signal per condition in a non-overlapping time windows of 9 s (Petkova and Ehrsson, 2008). In particular, we expected an increase in the GSRs following the threatening stimulus in the congruent as compared to the incongruent condition.

Proprioceptive drift. Prior to and upon completion of the experiment, all the subjects completed the proprioceptive drift test which followed a standard technique, see for instance (Sanchez-Vives et al., 2010). Specifically, the participants were asked to point to the location of the tip of their left index finger with the right index finger with no visual feedback available. The error in pointing (Tsakiris and Haggard, 2005) was computed as the distance between the two locations (the actual location of the tip of the left index finger and the pointing location) and measured in centimeters. We subtracted baseline responses from post-experimental errors for each participant. We expected stronger proprioceptive recalibration, and therefore, higher pointing errors in the congruent as compared to the incongruent condition.

Self-reports. At the end of every session, all participants completed a questionnaire which evaluated the subjective perception of body ownership and agency, adapted from a previous study (Kalckert and Ehrsson, 2012). The entire questionnaire consisted of twelve items (**Table 1**), six per domain (ownership and agency), three of which were related to the experience of ownership and agency, respectively, while the remaining served as controls. Participants answered each statement on a 7-point Likert Scale ranging from "–3": being in strong disagreement to "3": being in strong agreement. To counteract order effects, the sequence of the questions was randomized across all the subjects.

3. RESULTS

To test our hypothesis that action-driven purely distal cues which pertain to the task contribute to body ownership, we

TABLE 1 | The questionnaire, consisting of 12 statements divided into four different categories.

Category	Question
Ownership	I felt as if I was looking at my own hand
	I felt as if the virtual hand was part of my body
	I felt the virtual hand was my hand
Ownership control	It seemed as if I had more than one left hand
	It appeared as if the virtual hand were drifting toward my real hand
	It felt as if I had no longer a left hand, as if my left hand had disappeared
Agency	The virtual hand moved just like I wanted it to, as if it was obeying my will
	I felt as if I was controlling the movements of the virtual hand
	I felt as if I was causing the movement I saw, and the control questions were
Agency control	I felt as if the virtual hand was controlling my will
	I felt as if the virtual hand was controlling my movements
	I could sense the movement from somewhere between my real and virtual hand

used a virtual reality-based experimental setup (**Figures 1A, B**) where subjects were to complete a goal-oriented task, and manipulated the congruency of auditory action outcomes (**Figure 1E**). The experimental protocol (**Figure 1D**) consisted of three phases: the training block, (2) the experimental block in either congruent or incongruent condition, and (3) the threatening event (**Figures 1D, C**). To quantify body ownership, for each experimental session, we measured proprioceptive drifts, recorded Galvanic Skin Responses (GSR) to an unexpected threat, and administered self-reports. To measure performance, we computed scores, directional errors, and reaction times. For the analysis, we used t-tests and calculated Cohen's d to evaluate differences between conditions and the associated effect sizes.

3.1. Motor Control

Firstly, our results showed that the normalized performance-scores (proportion of successful trials) were significantly higher in the congruent ($\mu = 0.35, sd = 0.47$) than in the incongruent condition ($\mu = 0.17, sd = 0.38$), [$t_{(14)}$= 8.89, $p < 0.001$, d = 0.42] (**Figure 2A**). To explore the effects of the congruency of purely distal signals on performance, we compared both conditions in terms of directional errors (**Figure 2B**). In particular, a T-test indicated that the errors were significantly higher in the incongruent ($\mu = 6.42, sd = 4.52$) than in the congruent condition ($\mu = 3.30, sd = 2.01$), [$t_{(14)}$ = 19.52, $p < 0.001$, d = 0.89] (**Figure 2C**). To further investigate the relationship between the quality of the distal cues and performance, we averaged and compared the directional errors following the three types of auditory manipulations (**Figure 2D**). This analysis was performed exclusively for the incongruent condition. Interestingly, we found no difference between the distinct auditory cues including spatial ($\mu = 10.17, sd = 13.33$), temporal ($\mu = 7.99, sd = 9.75$) and semantic ($\mu = 7.22, sd = 7.23$) cues (**Figure 2D**). Specifically, a Kruskal-Wallis test indicated that all manipulations had the same significant effect on body ownership [${x^2}_{(2)}$ = 1.74, p = 0.39]. In addition, we observed that the congruency of the distal cues had no significant effect on the averaged reaction times when comparing the incongruent group ($\mu = 0.48, sd = 0.05$) with the congruent group ($\mu = 0.51, sd = 0.01$), $p = 0.46$ (**Figure 2E**).

3.2. Body Ownership

Prior to the appearance of the knife (10s baseline), the skin conductance was not different between the two groups [$t_{(14)} = 0.60, p = 0.55$; $\mu = 181.12, sd = 112.43$ for the congruent condition and $\mu = 230.25, sd = 183.75$ for the incongruent condition]. The analysis revealed, however, that the post-threatening stimulus GSR was significantly higher in the congruent ($\mu = 42.54, sd = 33.98$) than in the incongruent group ($\mu = 29.67, sd = 26.82$) [$t_{(14)} = 21.03, p < 0.001, d = 0.42$] (**Figures 2F, G**). Similarly, we found a difference in the proprioceptive drift between the congruent ($\mu = 4.88, sd = 2.36$) and incongruent group ($\mu = 1.5, sd = 1.51$) such that the errors in were significantly higher in the congruent condition [$t_{(14)} = 3.4, p = 0.004, d = 1.7$] (**Figure 2H**). We further report a statistically significant difference in the self-reported experience of ownership between the two conditions [$t_{(14)} = 4.97, p < 0.001, d = 2.5$]. The ownership ratings in the congruent group ($\mu = 1.13, sd = 0.56$) were greater than in the incongruent group ($\mu = -1.3, sd = 1.25$). We found no difference between the congruent ($\mu = -1.33, sd = 1.46$) and the incongruent group ($\mu = -1.3, sd = 1.25$) for the three control items [$t_{(14)} = 1.79, p = 1.38$]. We later analyzed questions related to agency. The results showed differences neither for the control questions [$t_{(14)} = 0.22, p = 0.82$] between congruent ($\mu = -1.67, sd = 1.49$) and incongruent condition ($\mu = -1.83, sd = 1.48$) nor for the experimental ones, congruent ($\mu = 1.5, sd = 1.13$) and incongruent condition ($\mu = 1.33, sd = 1.48$). In both groups participants experienced high agency during the experiment.

3.3. Relationship of the Ownership Measures

We assessed the relationship between the objective, subjective and behavioral ownership measures and, per each participant in both conditions, we computed: (1) mean GSR from 9 s post-threat, (2) mean of the three ownership questions; and (3) baseline-subtracted proprioceptive drift. The Spearman rank-order correlation between post-threat GSR and self-reported ownership was close to significance ($r = 0.47; p = 0.06$) (**Figure 3A**). However, we report high and significant positive correlation between the proprioceptive drift and self-reported ownership ($r = 0.75; p < 0.001$) (**Figure 3B**) as well as between the post-threatening GSR and proprioceptive drift ($r = 0.52; p < 0.03$) (**Figure 3C**).

4. DISCUSSION

In this study, we asked whether body ownership depends on the consistency of task-relevant purely distal sensory cues which result from self-initiated actions. In particular, we investigated the influence of those cues on performance and ownership using an embodied, virtual reality-based goal-oriented task where action outcomes were signaled by distinct auditory signals. We manipulated the congruency and therefore the predictability of those reafferent sensory signals and hypothesized that the (in)congruency of visuoauditory stimuli would affect both performance and body ownership. Our results support our prediction and suggest that both are compromised when action-driven purely distal signals are incongruent.

The plasticity of body ownership relative to the spatiotemporal coincidence of exafferent and reafferent multisensory signals has been well-accepted (Botvinick and Cohen, 1998; Craig, 2002; Tsakiris, 2010; Blanke, 2012; Seth, 2013; Suzuki et al., 2013). In particular, neurophysiological and behavioral studies have demonstrated that the experience of ownership is established through bottom-up integration and top-down prediction of proximodistal cues within the peripersonal space (Rizzolatti et al., 1981; Makin et al., 2007; Tsakiris, 2010; Blanke, 2012). Crucially, however, depending on whether the sensory signals are externally (classical Rubber Hand Illusion, RHI) or self-generated (*moving* Rubber Hand Illusion, mRHI and moving Virtual Hand Illusion, VHI), the top-down expectation signals seem to be qualitatively different. On the one hand, in the

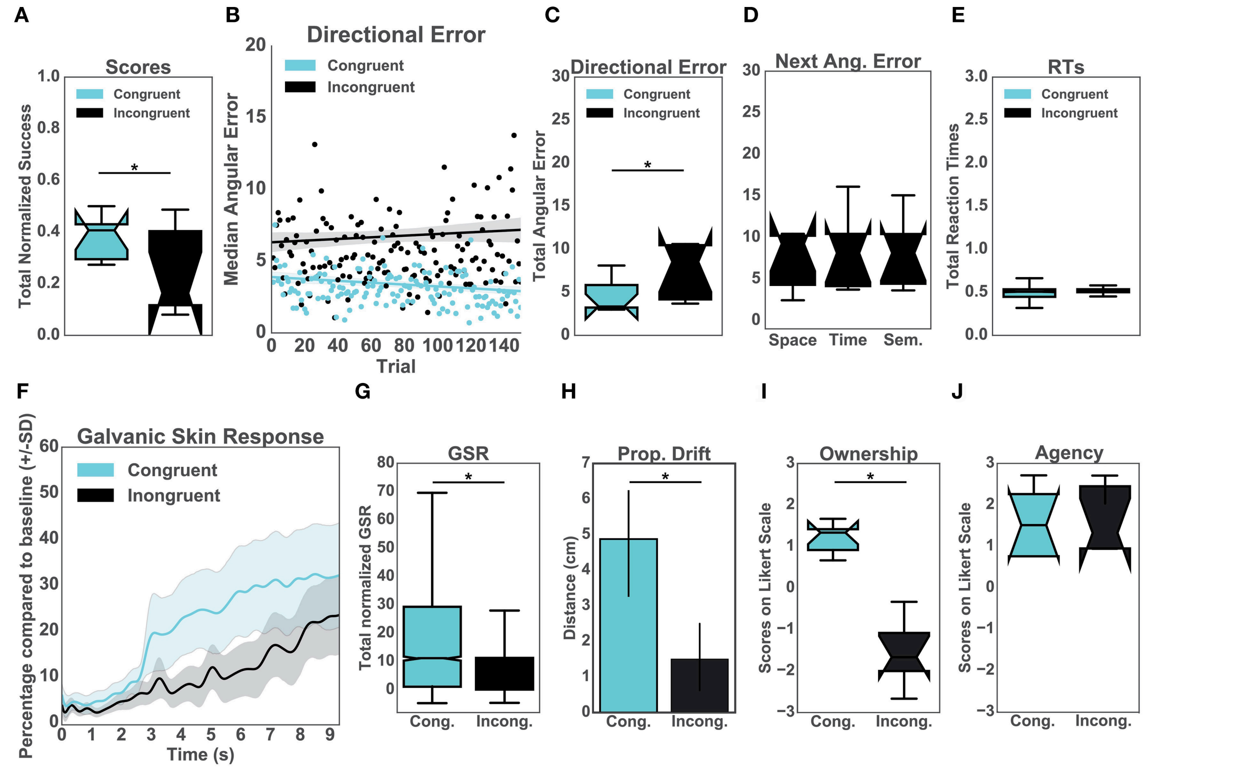

FIGURE 2 | Upper panel: Performance. **(A)** Normalized percentage of successful trials per group. **(B)** Median directional error per trial over the experimental block (*N* = 150) split per condition **(C)** Total directional error from all the trials per subject per condition. **(D)** This graph represents the mean values for the incongruent group only. In particular, the effects of the three auditory manipulations (spatial, temporal, and semantic) on the mean directional error on the consecutive trials. **(E)** Mean reaction times from all trials per condition. **Lower panel**: Body Ownership. **(F)** Galvanic Skin Response (GSR). The sampling rate for the GSR signal was 60 Hz. Accordingly, the data was run through a low-pass filter with a cut-off frequency of 3 Hz. The plot represents the mean GSR and the associated standard deviation for all participants in a time window of 9 s (Hägni et al., 2008), split per condition. The threatening event happened at time 0. **(G)** Mean GSR from 9 s post threatening event. **(H)** Proprioceptive drift. Results of the difference between pre- and post-test calculated in centimeters per condition. **(I)** Score from the self-reported experience of body ownership per group. Scores above 0 indicate ownership. **(J)** Score from the self-reported experience of agency per group. Scores above 0 indicate the experience of agency.

RHI, the sensory correlations are modulated by top-down influences which constitute empirically induced priors related to the internal model of the body (Tsakiris and Haggard, 2005; Costantini and Haggard, 2007; Lloyd, 2007; Makin et al., 2008). For instance, the illusion of ownership will not occur if the shape or the location of the fake hand is not plausible (Tsakiris, 2010). On the other hand, the evidence from the mRHI and VHI supports that, in the contexts of self-generated stimuli, body ownership is actively shaped by top-down processes allowing for continuous comparison between the actual and predicted action-consequences from proximodistal modalities (Dummer et al., 2009; Sanchez-Vives et al., 2010; Ma and Hommel, 2015a,b). In fact, when the errors in those sensory predictions (the so-called Sensory Prediction Errors, SPE) are insignificant, that is, when the visual feedback of the position of the rubber (mRHI) or virtual (VHI) hand is congruent with the proprioceptive cues, the ownership over the artificial arm is high, and vice versa (Dummer et al., 2009; Sanchez-Vives et al., 2010). Contrary to the standard RHI, in the mRHI and VHI, the physical, spatial and temporal characteristics of the body do not influence the experience of ownership (Banakou et al., 2013; Peck et al., 2013; Ma and Hommel, 2015b; Romano et al., 2015; Van Dam and Stephens, 2018). Moreover, it has been demonstrated that participants can perceive an actively operated virtual non-corporeal and 'disconnected' object (balloon or a square) as an extension of their own body as long as it follows the predicted trajectory Ma and Hommel (2015a). Thus, when acting in the world, the top-down predictive processing modulating ownership seems not to depend on the generative models of self but rather on the forward models (or corollary discharge) which guide action by generating sensory predictions about the consequences of movement based on the efference copy (Miall and Wolpert, 1996; Sanchez-Vives et al., 2010; Ma and Hommel, 2015b; Kilteni and Ehrsson, 2017). Similar, from the perspective of ideomotor theory, ownership might be viewed as depending on the difference between the goals (intended action effects) and the perceptual consequences (actual action effects) (Stock and Stock, 2004; Hommel, 2009; Shin et al., 2010).

Ample research demonstrates that the central nervous system uses forward models for the differential processing of the predicted and the actual reafferent information which was shown to underlie motor control and agency (Wolpert et al., 1995; Miall and Wolpert, 1996; Bäß et al., 2008; Crapse and Sommer, 2008; Sommer and Wurtz, 2008; Schwarz et al., 2018). Crucially, the internal (forward) models do not exclusively process sensory signals related to the body, but they integrate across all sensory information from both proximal (proprioceptive, tactile) and distal (visual, auditory) modalities (Jordan and Rumelhart, 1992; Miall and Wolpert, 1996). This would suggest that, if body ownership results from a consistency of forward models, it will be affected by the(in)congruency of not only proximodistal cues such as in the moving rubber hand illusion or the virtual hand illusion (Dummer et al., 2009; Sanchez-Vives et al., 2010) but also purely distal signals given that they constitute information about the action-consequences. In this study, we explicitly addressed this question using a variation of a VHI paradigm, which required the participants to perform actions that triggered distal (auditory) cues. Those auditory cues indicated the location and the time of a collision of a puck with the walls or the goal as well as the outcome (failure or success). To test whether action-driven and task-relevant sensory signals impact body ownership, in one of the groups, we manipulated their congruency. We predicted that the ownership scores, measured subjectively, objectively and behaviorally could be lower in the condition where the cues do not match predictions about purely distal sensory signals.

Did the proposed purely distal cues affect body ownership? Results from all the ownership measures (**Figure 2**, Lower panel: Body Ownership), including skin conductance (GSR), proprioceptive drift and the questionnaire support that purely distal cues which pertain to the task and violate predictions about the auditory action outcomes compromise body ownership. Specifically, we found that the scores were significantly higher in the congruent compared to the incongruent condition in all analyses (**Figure 2**, Lower panel: Body Ownership). Subsequent correlations between the proposed measures (**Figure 3**) further confirmed the consistency of the obtained results within three dimensions of ownership quantification including physiological response, behavioral proprioceptive recalibration, and a conscious report (Longo et al., 2008). Similar to the mRHI, VHI (Sanchez-Vives et al., 2010; Ma and Hommel, 2015b) and their variations (i.e., Ma and Hommel, 2015a), here we interpret the obtained low-ownership outcome in the incongruent condition (**Figure 2**, Upper panel: body Ownership) as a consequence of high sensory prediction errors possibly computed but the forward model (Miall and Wolpert, 1996; Crapse and Sommer, 2008; Limanowski and Blankenburg, 2013; Apps and Tsakiris, 2014). In our case, however, the sensory conflicts were driven by a discrepancy between the predicted and actual purely distal visuoauditory signals which did not pertain to the body but were relevant to the outcome of the goal-oriented task. We speculate that the manipulation of the proposed signals might have reflected on the errors of the forward models which influence performance and possibly body ownership (Wolpert et al., 1995). This could further suggest that the integration of signals from distal modalities might affect the integration of signals from proximal or proximodistal modalities establishing a feedback loop. In such case, any (in)congruent relationship between distal, proximodistal, and proximal signals which pertain to the goal of the task would affect the experience of ownership and even define the boundaries of the embodied self. To the best of our knowledge, our results propose for the first time that the ownership of a body might be driven by bottom-up integration and top-down prediction of purely distal modalities occurring outside of the body and outside of the peripersonal space (Rizzolatti et al., 1981). This would support recent findings which suggest that body ownership is coupled to the motor systems and that, similar to the experience of agency, it might depend on the congruency of a forward model or corollary discharge (Ma and Hommel, 2015b; Grechuta et al., 2017; Kilteni and Ehrsson, 2017). As expected, the visuoauditory manipulations did not significantly influence the perceived agency (**Figure 2J**). Participants reported control over the virtual hand in both conditions, probably due to the congruent mapping of the proximal cues (see Methods section about the sensory manipulations). The visual feedback of the movement of the arm always followed the desired trajectory, which is one of the

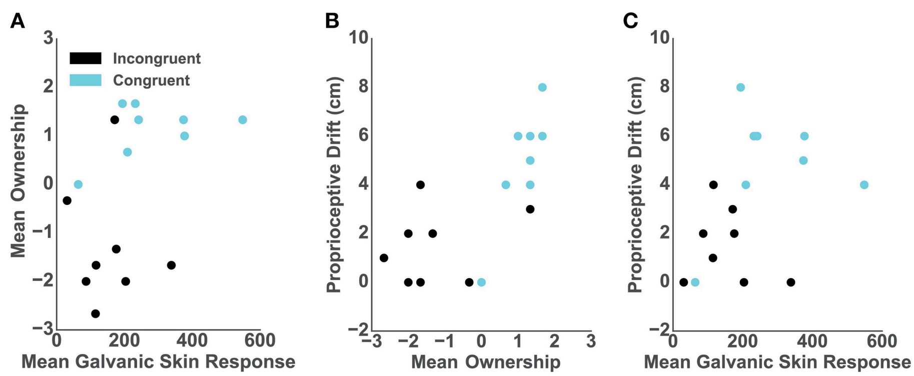

FIGURE 3 | Correlations. In all graphs dots represent individual participants and colors represent conditions: blue- congruent and black- incongruent. **(A)** Mean GSR 9 s post-threatening event and mean self-reported ownership. **(B)** Mean self-reported ownership and the proprioceptive drift score. **(C)** Mean GSR 9 s post-threatening event and the proprioceptive drift score.

three questions addressed in the standard self-reported agency assessment (Kalckert and Ehrsson, 2012).

At the current stage, two questions remain open. First, how can the integration of distal and proximodistal cues occur in the service of body ownership? Since the primary purpose of the present study was to investigate the influence of purely distal signals on body ownership, the proximodistal (visuo-proprioceptive) cues within the peripersonal space were congruent in both groups. Indeed, based on those cues, participants could always predict the location and the time of the distal auditory signals (spatial and temporal manipulation) as well as the outcome of an action (semantic manipulation). Therefore, in the incongruent condition, where the distal consequences of the actions did not match the predictions, we expected that the sensory prediction errors would negatively impact ownership. However, with the current design, we can neither explain the interaction of the proximodistal and distal cues nor how do they weight the experience of ownership. Future studies should further investigate the relationship between the visual and auditory cues and their relative impact on body ownership by, for instance, manipulating visuomotor and visuoauditory feedback independently during a motor task. A recent Hierarchical Sensory Predictive Control (HSPC) theory proposes a cascade of purely sensory predictions which mirror the causal sequence of the perceptual events preceding a sensory event (Maffei et al., 2017). In the context of anticipatory control, this control architecture acquires internal models of the environment and the body through a hierarchy of sensory predictions from visual (distal) to proprioceptive and vestibular modalities (proximal). If body ownership and motor control share the same forward models, which comprise both distal, proximodistal, and proximal signals, ownership might be realized through a similar cascade of sensory predictions. In our case, however, which includes a goal-oriented task and voluntary control, the internal models might be acquired from the proprioceptive and vestibular modalities (proximal) to visual (distal), a hypothesis yet to be investigated. In such case, one could expect differences in reaction times between the congruent and the incongruent conditions due to increased sensory prediction errors. Interestingly, our results yielded no differences in the reaction times between the groups. We believe that this result might depend on the congruency of proximodistal signals. Specifically, the visual feedback of the movement always matched the proprioceptive cues. It is possible that for motor control the prediction errors from the proximodistal modalities are more relevant (they are weighted higher) than those from purely distal. We suggest that future studies should systematically investigate the contribution of different cues to performance, possibly within the framework of HSPC (Maffei et al., 2017). Second, if body ownership depends on the consistency of internal models, and therefore on the accuracy of sensory predictions, could task-irrelevant signals manipulate it? While playing Air Hockey, the brain does not only integrate action-driven sensory signals but also simultaneously processes purely external action-independent information which derives from the environment. This information might well include corrective information and, therefore, be relevant to the task (i.e., the wind which affects the trajectory of the puck) or not (i.e., time of the day) (Shadmehr et al., 1994). Changing the rules of the environment and investigating the experience of ownership and performance when action-independent (task-irrelevant) sensory expectations are violated would shed light on the nature of sensory signals relevant for the processing of self as well as their underlying mechanisms (i.e., generative and forward models) (Friston, 2012; Seth, 2013; Apps and Tsakiris, 2014).

What is the role of purely distal action-driven cues in goal-oriented behavior? Our results demonstrate that performance, as measured through the overall scores (**Figure 2A**) and directional errors (**Figures 2B, C**), was significantly hampered in the incongruent compared to the congruent condition. Importantly, these results did not depend on differences in reaction times (**Figure 2E**) suggesting no influence of possible attentional biases (i.e., distractions) in either of the groups. On the one hand, this outcome might be interpreted within the framework of computational motor control. The reported differences in performance between the two conditions could have been influenced by the discrepancies between the efference copies of distal events and the actual action outcomes. Indeed, results from motor control studies support the notion that learning (progressive reduction of error) depends on both proximal and distal sensory prediction errors that allow for adjustments and anticipation of possible perturbations deriving from the body and environment (Jordan and Rumelhart, 1992; Mazzoni and Krakauer, 2006; Tseng et al., 2007; Krakauer, 2009; Maffei et al., 2017; Morehead et al., 2017). As a result, during action execution, inputs from all the sensory modalities are transformed into error signals updating the forward model and, consequently, future behavior (Wolpert and Kawato, 1998; Kawato, 1999; Shadmehr et al., 2010; Wolpert et al., 2011). In our experiment, the directionality of the error indicated by the spatial distribution of the sound, the speed of the puck indicated by the temporal characteristics of the sound, as well as the knowledge of results all constituted error signals which could supervise corrective motor commands. Crucially, while the spatial and temporal dimensions provided information about the action parameters on a continuous range, the semantic dimension constituted a binary reinforcement signal informing about a failure or a success. As such, the chosen audiovisual cues in the incongruent condition might have influenced performance, which, in turn, affected body ownership. In fact, clinical studies provide evidence that patients suffering from hemiparesis, whose motor function is reduced due to stroke, progressively stop using the paretic limb: the so-called learned non-use phenomenon (Taub et al., 2006). In this, and other neurological cases, a prolonged lack of use (low performance) often causes disturbances in the sense of ownership and agency (Gallagher, 2006) supporting a hypothesis that there might be a causal effect between performance and body ownership. The present design which includes three types of sensory manipulations pseudorandomly distributed within each block does not allow us to disambiguate between the specific contribution of each of the manipulations. A systematic study on the influence of individual sensory signals, including the three manipulations, would help to better understand the mechanisms accounting for low-performance scores in the incongruent condition. An alternative interpretation of our results is related to the experimental and theoretical framework of body ownership. Several studies propose that body ownership is coupled to the motor system such that it updates the sensory representation of the body and provides inputs to the forward model. The forward model, in turn, generates and updates predictions relative to both the body and the environment during voluntary actions (Kilteni and Ehrsson, 2017), reinforcing the history of sensorimotor contingencies. In particular, we find evidence that body ownership is involved in generating body-specific predictions about the sensory consequences of voluntary actions thus determining somatosensory attenuation (Kilteni and Ehrsson, 2017). This finding is consistent with another study which employed a standard RHI in virtual reality and demonstrated that ownership is correlated with motor performance during a perceptual decision-making task (Grechuta et al., 2017). Contrary to the previous discussion, in this case, ownership would have a modulatory effect on performance.

At the current stage, we cannot disambiguate between the two alternative hypotheses and determine whether the integration of purely distal cues influences ownership and performance in parallel or independently and what is the directionality. We demonstrate, however, that both depend on the congruency of action-driven and task-relevant purely distal signals, which supports the notion that both rely on the consistency of forward models driving goal-oriented action (Seth, 2013; Apps and Tsakiris, 2014). We expect that this outcome will allow for the advancement of our understanding of the mechanisms underlying body ownership. To improve the experimental quality of the present study and further support our findings, future studies shall consider a bigger sample size as well as an alternative objective measure of ownership (i.e., body temperature) which would allow for conducting a within-group experiment without biasing the physiological signals (Moseley et al., 2008). Finally, the reported finding might find applications in fields such as motor training simulators and rehabilitation. For instance, virtual reality-based treatments of post-stroke motor disorders (Cameirão et al., 2010; Grechuta et al., 2014; Mihelj et al., 2014; Ballester et al., 2015) might benefit from a design of reliable and spatiotemporally congruent environments which may positively impact the ownership of the virtual body as well as performance possibly impacting recovery. Further clinical studies should evaluate the same principle in rehabilitation protocols for ownership disturbances following acquired brain lesions including neglect (Coslett, 1998), anosognosia for hemiplegia (Pia et al., 2004) or somatoparaphrenia (Fotopoulou et al., 2011).

ETHICS STATEMENT

The protocol was approved by the ethical committee of the University of Pompeu Fabra (Barcelona, Spain). All subjects provided their written informed consent.

AUTHOR CONTRIBUTIONS

KG, LU, and BR designed the protocol, KG and LU conceived the experiment and LU conducted the experiments, KG and LU analyzed the results, KG, LU, and PV wrote the manuscript. PV initiated and supervised the research. All authors reviewed and approved the manuscript.

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Analysis of Perceptual Expertise in Radiology – Current Knowledge and a New Perspective

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Radiologists rely principally on visual inspection to detect, describe, and classify findings in medical images. As most interpretive errors in radiology are perceptual in nature, understanding the path to radiologic expertise during image analysis is essential to educate future generations of radiologists. We review the perceptual tasks and challenges in radiologic diagnosis, discuss models of radiologic image perception, consider the application of perceptual learning methods in medical training, and suggest a new approach to understanding perceptional expertise. Specific principled enhancements to educational practices in radiology promise to deepen perceptual expertise among radiologists with the goal of improving training and reducing medical error.

Keywords: visual perception, expertise, radiology, visual search, perceptual learning, attention, holistic processing, gist

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INTRODUCTION

Optimizing perceptual expertise in radiology has great practical importance. One of the primary goals of radiology education is to train novices to develop advanced or 'expert' search methods to enhance abnormality recognition (Wood, 1999). The principles underlying radiologic expertise are also important beyond the immediate field as courts and policy makers rely on radiologists to provide testimony and educate juries on applicable standards of medical care (Andrew, 2006; Berlin et al., 2006). Despite continual efforts to refine radiology education, however, the error rate in radiological readings has not improved in the last seven decades (Garland, 1949; Berlin, 2007), persisting at a rate of approximately 33% for abnormal studies (Waite et al., 2017b). This problem—compounded by increasing imaging volumes and examination complexity—mandates a deeper understanding of the nature of radiological expertise, to improve both student training as well as the accuracy of practicing clinicians.

In this review we put forward that radiology's error rate has been recalcitrant to improvement secondary to a lack of knowledge about the mechanisms of expertise. We further propose that no principled theories for improvement will be developed until we understand the precise nature of expertise in radiology. We discuss the definition of perceptual expertise in radiology, search strategies employed by experts, and current training methods. We also examine the limitations of extant eye tracking studies and visual processing theories regarding radiological expertise.

Finally, we delineate a new approach to achieve a principled understanding of radiologic expertise, and how it will promote new heuristics (i.e., in designing individualized educational plans for each radiological trainee), with the ultimate goal of reducing radiological error (Gegenfurtner et al., 2017; Sheridan and Reingold, 2017; Waite et al., 2017b).

WHAT DOES RADIOLOGIC EXPERTISE MEAN?

Radiologists are physicians who specialize in diagnosing and treating disease using a variety of medical imaging techniques such as x-rays, computed tomography (CT), magnetic resonance imaging (MRI), Positron emission tomography (PET), and ultrasound. In addition to a continually growing body of 'fact-based' knowledge regarding anatomy, radiological pathology, physics, and clinical medicine, expertise in radiology is considered largely perceptual in nature, defined by refined visual search patterns and diagnostic accuracy (Kelly et al., 2016). Thus, expert radiologists not only perceive abnormalities that non-experts do not, but they also better understand what to attend to and what to ignore (Gunderman and Patel, 2019).

Expertise in diagnostic imaging is usually inferred from the physician's rank within the medical hierarchy—their title, level of training (i.e., intern, resident, attending, specialist), and years of experience—rather than by objective metrics. These indirect measures are presumably relied on because is difficult to accurately measure expertise. A principled understanding of perceptual expertise in specific tasks such as abnormality detection in radiology does not exist. If we could assess expertise with a biomarker instead —irrespective of physician's rank— it would not only provide the basis to maximize accuracy and optimize heuristics, but it would also help determine the importance of training versus that of natural aptitude.

ANALYSIS OF MEDICAL IMAGING

At a fundamental level, image analysis involves two basic processes: visual inspection of the image and interpretation (Krupinski, 2010). Broadly, diagnostic radiology entails (1) detection—noting a potentially significant finding is present that merits further analysis; (2) recognition—deciding that the finding is pathologic; (3) discrimination—characterizing the lesion as a specific type; and (4) diagnosis. The first task, detection, has primary importance, because all following steps leading to diagnosis rely on detection efficacy (Gray et al., 1978).

Perception is paramount in radiologic diagnosis because if a radiologist misses an abnormality, no amount of factual knowledge can remedy such a lapse; the diagnostic process may be prematurely terminated, resulting in misdiagnosis and subsequent harm to the patient. At the other end of the spectrum, false positives can also be detrimental to patient health. In both cases, until we better understand the nature of radiologic expertise, we will not be able to dissociate the contributions of perception and cognition to diagnostic accuracy.

ERROR RATES IN RADIOLOGY

Garland (1949) found that radiologists incurred an error rate of 33% in the interpretation of *positive* films (films that contain an abnormality), measured against the consensus of a group of experts. In a typical clinical practice (comprised of both normal and abnormal studies), the diagnostic error rate is approximately 4% (Siegle et al., 1998), a rate that translates into approximately 40 million interpretive errors per year worldwide (Bruno et al., 2015). Since Garland's pioneering study, significant error rates have been noted in varied plain film modalities including mammography, chest X-rays (CXR), and bone X-rays, involving radiologists not only in private practice (Siegle et al., 1998), but also in academic settings, where interpretive error rates range from 13 to 90% depending on experimental conditions and the functional definition of error (Garland, 1949; Lehr et al., 1976; Forrest and Friedman, 1981; Muhm et al., 1983; Berlin, 2007; Brady, 2017). Recent studies of new technologies in radiology have determined that high error rates also exist in CT, MRI, and Ultrasound interpretation (Berlin, 2014; Herzog et al., 2017; Banaste et al., 2018).

Because of the subjective nature of radiologic interpretation, the definition of what is erroneous is established by expert opinion (Waite et al., 2017b). Thus, in a conclusive 'error' (as opposed to acceptable variation across observers), there is a substantial discrepancy with respect to peer consensus (Waite et al., 2017b). Although radiologic error can be classified in a number of ways (Kim and Mansfield, 2014), two broad categories of interpretive error are usually identified: perceptual errors and cognitive errors (Bruno et al., 2015). Cognitive errors are considered to occur when a correct positive finding is followed by misclassification due to faulty reasoning or lack of knowledge (Renfrew et al., 1992). Communication errors are an additional important cause of error, outside of interpretive or perceptual categorization (Waite et al., 2017c, 2018).

Omission or false negative errors occur when a radiologist fails to notice a perceptible lesion (as opposed to a fundamentally ambiguous lesion). A major source of diagnostic error and litigation, omission errors have been divided into three categories based on fixation times on missed lesions: search, recognition, and decision-making. Search errors are scanning errors in which the observer never fixates the lesion. Recognition errors are omission errors where the radiologist fixates the lesion for a duration shorter than the threshold dwell time (from 500 to 1000 ms depending on modality) considered necessary to recognize lesion features, and therefore fails to identify it. Decision-making errors are omission errors where the radiologist fixates the lesion for long enough to extract relevant lesion features, but dismisses the lesion as inconsequential (Kundel et al., 1978; Krupinski, 2010). Although only search and recognition errors are technically perceptual in etiology (Krupinski, 2010; Waite et al., 2017b), given the lack of eye tracking metrics during routine clinical imaging and most research studies, in practice (and in this review) all omission errors are usually termed 'perceptual' (Bruno et al., 2015).

Renfrew et al. (1992) classified 182 cases presented at a problem case conference and found that 43% were secondary to false negative or false positive readings. Kim and Mansfield analyzed 656 radiologic examinations with delayed diagnosis secondary to radiologic error and found that 42% were secondary to missed diagnosis ('under-reading') *without* an identifiable cause. An *additional* 42% were also secondary to missed diagnosis, but were felt to be attributable to a variety of causes, including satisfaction of search—where lesions remain undetected after the discovery of an initial lesion, alliterative error—where an error is made secondary to overreliance on a prior report, poor/misleading history, location of a finding outside the field of interest or at the corner of a film, and failure to consult prior radiologic studies/reports (Kim and Mansfield, 2014). In an analysis of 496 suits leading to malpractice claims, failure to diagnose was overwhelmingly the most common reason for initiating a malpractice suit against radiologists, comprising 78% of the cases (Baker et al., 2013). Funaki et al. (1997) and Rosenkrantz and Bansal (2016) found that missed findings accounted for 60–80% of interpretive error. Thus, faulty detection—failure to identify salient findings—is considered the most important source of interpretive error in radiology (Degnan et al., 2018).

Less discussed in the literature, false positive errors are also important to recognize. A major problem in screening examinations, false positive errors cause patient anxiety and often engender further unnecessary studies and procedures (Castells et al., 2016).

Given their ubiquity, interpretive errors are unlikely to be entirely due to bad radiologists (Brady, 2017). Indeed, given the high incidence of interpretive errors in essentially all radiologic scenarios—across multiple imaging modalities, and in both private practice and academic settings—a more probable explanation is that the methods to select potential radiology trainees, and resident education, are not better nowadays than 70 years ago.

ATTENTION AND PERCEPTION

Voluntary attention—the selective processing of information at a given location—is deployed with specific targets in mind and guided to target locations by their prominent visual features (Wolfe et al., 1989; Wolfe, 1994; Alexander and Zelinsky, 2009, 2011; Carrasco, 2011, 2014; Eckstein, 2011; Anton-Erxleben and Carrasco, 2013; Carrasco and Barbot, 2014; Nobre et al., 2014). Whereas color, brightness, and motion are known to attract attention in a bottom–up manner (Wolfe et al., 2016; Wolfe and Horowitz, 2017), the observer's intended target representation also directs attention in a top–down manner. Learning, memory, and expectations shape this process (Carrasco et al., 1998; Chen and Zelinsky, 2006; Wolfe et al., 2016). Thus, radiological search likely reflects a combination of bottom–up and top–down attention (Jampani et al., 2012; Wen et al., 2017).

By developing better target representations—for example, with increasing expertise in nodule detection—radiologists learn to remove many irrelevant areas from consideration, based on their understanding of the structure and content of radiological images (Wolfe et al., 2016). Thus, expert radiologists do not scrutinize all regions of the image equally but direct their attention and eye movements more precisely to relevant areas. This heightens efficiency but can also mask unexpected findings.

EYE MOVEMENTS AND SEARCH PATTERNS IN RADIOLOGY

Eye Movements and Expertise

The study of eye movements can reveal not only the cognitive processes behind expertise, but also the mechanisms involved in acquiring these skills. In addition, studies of expert gaze patterns can identify common perceptual errors leading to strategies to mitigate them– improving training and reducing error (Fox and Faulkner-Jones, 2017). As such, eye tracking technology has been increasingly used to understand the nature and acquisition of radiological expertise.

During interpretation, expert radiologists generally fixate on abnormalities faster than novices, and their total image search time decreases with increasing levels of expertise (van der Gijp et al., 2017a). Experts also have fewer total fixations than novices. These differences may be due to novices spending more time looking at irrelevant but salient structures [such as the heart on a chest x-ray (CXR), when the lungs are more important to analyze in a nodule detection task] with experts demonstrating more effective search secondary to refined scene guidance (Wolfe et al., 2016; van der Gijp et al., 2017a). Other gaze metrics, such as saccade length and image coverage, demonstrate less consistent experience-based differences across studies (van der Gijp et al., 2017a) (**Figure 1**).

Although most studies have examined the effects of expertise on plain film interpretation, expert radiologists are also more accurate and faster than novices during interpretation of *volumetric* imaging (Nakashima et al., 2016). In a study evaluating accuracy and interpretation in stroke CT and MRI cases, Cooper et al. (2009) found that attending radiologists were more accurate and had decreased time to fixation on lesions compared with novices. In addition, novices spent more time than experts examining normal anatomy, such as the ventricles (Cooper et al., 2009). Mallett et al. (2014) found that experts viewing a CT colonography video had shorter time to first pursuit on polyps (defined as the time from the beginning of video to fixation on the polyp for longer than 100 ms) compared with novices. A study of abdominal CT similarly found that attendings had higher accuracy than residents (Bertram et al., 2016). Another study found that experts had increased sensitivity toward medically important findings (such as nodules) compared with unimportant findings (such as bullae), suggesting specialization of their perceptual skills to detection of relevant findings (Nakashima et al., 2015).

Bertram et al. (2016) found that, whereas attendings and advanced residents performed better than less experienced residents when detecting low-contrast lesions on CT, detection of high-contrast lesions was comparable across groups. This finding suggests that expertise results in an increased ability to detect less salient abnormalities (Bertram et al., 2016).

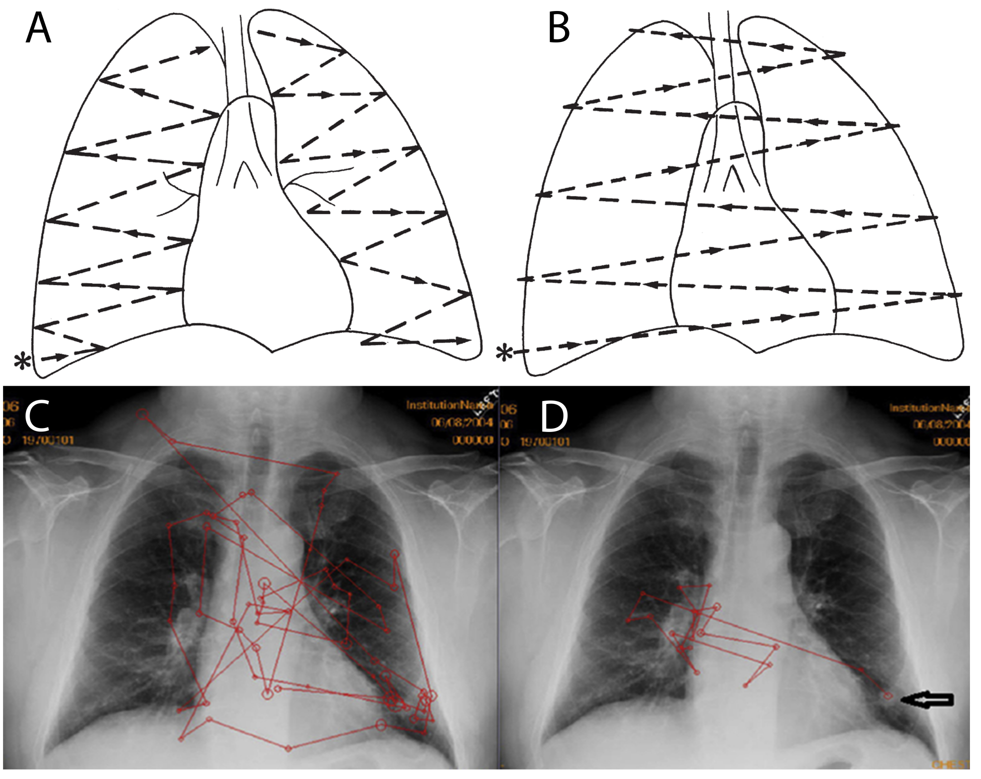

FIGURE 1 | Reprinted from Goodman and Felson (2007) with permission. **(A,B)** Proposed lung search pattern. **(A)** This commonly taught search pattern for examination of the lungs during chest radiograph (CXR) interpretation involves starting at the right base (*) (the costophrenic angle) and examining the right and then left lungs. **(B)** A second look is then performed in order to compare the right and left lungs as bilateral symmetry is assumed to be useful in recognizing abnormalities (Carmody et al., 1984). Reprinted from Waite et al. (2017a) with permission. Typical scanpaths of a novice **(C)** and an expert **(D)** radiologist, both searching a CXR which has a nodule at the left base (arrow in **D**). This free search pattern **(D)** is typically employed by experts and differs from the formal radiologic training given in residency. Instead, it indicates the flexible use of search strategies as a function of immediate visual information. The expert radiologist **(D)** has more efficient scanpaths (red lines) than the novice **(C)**, with fewer fixations (circles), less coverage of the image, fewer saccades, and faster arrival at the abnormality.

Relationship Between Fatigue, Expert Performance, and Eye Movements

Expertise may limit the effects of fatigue-related decreases in performance and changes in eye movements. Krupinski et al. (2012) found that residents had reduced detection accuracy in a CT nodule detection task after a day of reading, but the accuracy of attending radiologists was unaffected (Waite et al., 2017a). Similarly, Bertram et al. (2016) found that increased time at work resulted in decreased performance with CT scans for junior residents (with less than 2 years' experience), suggesting that enhanced mental effort is more robust to fatigue in expert readers.

Hanna et al. (2018) found that after an overnight shift fatigued radiologists demonstrated worse diagnostic performance (with increased false negatives and positives) and increased time to fixate on fractures when examining bone radiographs. Although total viewing time per case was longer for all radiologists when fatigued, the effect was significantly more pronounced with residents compared to faculty members. In effect, in their fatigued states, faculty members had eye-tracking parameters more characteristic of non-fatigued residents (Hanna et al., 2018).

Do High-Performing Radiologists Have Greater Preexisting Visuospatial Skills?

Given the possibility that ingrained aptitude could play a role in radiological success, measuring the perceptual abilities of radiology applicants and residents could be of great practical importance. The excellence of a group of professionals may be optimized through selection of individuals with the best requisite skill set. Radiology residency applicants are usually selected on the basis of academic records, letters of recommendation, and a short interview (Smith and Berbaum, 1991), none of which directly pertain to perceptual abilities. As Birchall notes, the existing model of training assumes that almost all trainees will eventually reach an acceptable standard with practice and semantic knowledge. Yet, it is possible that trainees with higher preexisting skills (i.e., in visual-spatial processing) may reach a *higher level* of expertise—or may achieve the highest level *more quickly*—than trainees with lower preexisting skills (Birchall, 2015). The identification of a relevant perceptual test might therefore help determine how much individual residents may benefit from training, and, ultimately, how they will perform as radiologists (Sunday et al., 2017).

The fact that radiology's high rate of error has remained unchanged for over half a century may be partly explained by selecting applicants without regards to their perceptual (or 'potential' perceptual) abilities. It is unknown whether high-performing radiologists had greater baseline visuospatial skills at the start of their training or whether their ability was secondary to learned expertise (Corry, 2011). The persistence of high interpretive error rates and the occasional 'spectacular failure' suggest the necessity of reevaluating selection methods (Smith and Berbaum, 1991).

To this end, investigators have attempted to identify perceptual requirements for both learning and practicing radiology, as well as whether practicing radiologists have superior perceptual skills outside of imaging. Nodine and colleagues conducted a series of experiments comparing the performance of radiologists and laypeople in searching Where's Waldo images from the popular children's books (in which the challenge for readers is to find the character Waldo amongst a crowd of people). Radiologists and laypeople performed similarly, indicating that radiological expertise in visual search and/or perceptual discrimination did not carry over to non-radiological tasks (Nodine and Krupinski, 1998).

Bass and Chiles performed a series of visual and perceptual tests (including tests of visual acuity, contrast sensitivity, visual memory, visual completion, gestalt closure, identification of hidden figures in a picture, and three-dimensional construction ability) in medical students, residents, and faculty (Bass and Chiles, 1990). They found a correlation between performance on the hidden figures test and the ability to identify pulmonary nodules on a CXR for medical students, but not for residents or board-certified radiologists, suggesting that any innate abilities are quickly superseded by training (Bass and Chiles, 1990).

Similarly, Kelly and colleagues found no difference in performance or gaze dynamics across radiologists of varying levels of experience (ranging from interns to attendings) when asked to identify hospitals on a series of maps, or to find an anomalous shape within a group of similar shapes. These results reinforce the premise that radiologic expertise is a learned task-specific skill (Kelly et al., 2018).

Smoker et al. (1984) found a correlation between radiology residents' ability to assemble Lego blocks by replicating a diagram and semiannual faculty ratings of their film reading performance. Because the results of the construction tests did not differ between residents and faculty with varied experience, the researchers concluded that the tests measured inherent aptitude rather than expertise (Smoker et al., 1984). Follow up studies confirming these preliminary results have not been performed, however, and no visuospatial ability test currently exists to determine whether someone is likely to become an 'expert' radiologist (Smith and Berbaum, 1991; Krupinski, 2011). Indeed, residency training programs do not objectively measure perception either before or during residency (Brazeau-Lamontagne et al., 2004). Unfortunately, taught declarative knowledge about *what* to look for does not ensure either expert perceptual abilities or act as a safeguard against 'creative reading' such as interpreting composite shadows as real nodules (Brazeau-Lamontagne et al., 2004).

A recent study by Sunday et al. (2017) found a modest correlation in naïve subjects between performance on the Vanderbilt Chest Radiograph Test (VCRT, where observers mark in which lung a nodule is when looking at two CXR's) and on the Novel Object Memory Test (a domain-general test of novel object recognition). Further research may determine whether some individuals learn to recognize radiologic abnormalities faster than others, and whether preexisting abilities, such as measured by the VCRT, place a limit on one's ultimate level of performance (Sunday et al., 2017).

Search Pattern Instruction for Plain Film Imaging in Radiology

Research findings concerning human perception of medical images have not been widely translated into practical heuristics that improve training (Auffermann et al., 2016). Although there are published guidelines on how to interpret various radiologic examinations (Puddy and Hill, 2007; James and Kelly, 2013), they tend to be unprincipled and subjective, with few studies demonstrating their efficacy. When systematically analyzed, most of these educational tools have had mixed results.

Because novices lack the ability to generate a rapid and accurate global impression of an image, they may benefit from an orderly and comprehensive search pattern/order (Goodman and Felson, 2007; Auffermann et al., 2016) (**Figure 1**). If readers adhere to a specific order or search pattern in the inspection of anatomical structures, they may achieve more complete coverage of the image, reducing the number of overlooked abnormalities. Although full coverage could also be achieved by inspecting anatomical structures in a *random* order, keeping a specific order of inspection provides readers with a mental checklist (Kok et al., 2015). Thus, one commonly taught technique, "systematic viewing," is to inspect anatomical areas in a fixed order.

Evidence to support the value of "systematic viewing" is wanting, however. Whereas, van Geel et al. (2017) found that students trained in systematic viewing methods inspected a larger portion of images than untrained students, they found no difference in their performance in chest radiographic interpretation. Kok et al. (2015) demonstrated similar findings. The combined data indicate that an emphasis on systematic viewing may not be justified.

Auffermann et al. (2016) found that physician assistants that were taught specific eye movements for analyzing CXR's improved their ability to identify nodules and made less identification errors than those without such training. However, this study did not track the eye movements of participants. Thus, the effects of eye-movement training on search patterns or image coverage remain unknown (van Geel et al., 2017).

Expert Search Patterns

One potential reason that pre-defined search patterns fail to consistently improve resident accuracy is that experts themselves do not read plain films in a consistent, standardized manner. Therefore, the various advocated search methods are not consistently used in practice (Kundel and La Follette, 1972)

(**Figure 1**). Instead, experts use a variety of non-systematic search patterns, so-called 'free search,' when looking at images (Auffermann et al., 2016). An evolution of search patterns from medical students to attending radiologists was noted in one study but attending search patterns were not systematic; eye movements were more affected by the findings on the radiograph than any preplanned search pattern (Kundel and La Follette, 1972). A pioneering study by Tuddenham and Calvert (1961) found a wide variation in search patterns among readers. Ironically, the only observer with a reproducible search pattern failed to report findings noted by observers with inconsistent patterns (Tuddenham and Calvert, 1961). These findings are remarkably consistent with those from studies conducted over 50 years later, suggesting that consistent search patterns do not help, and indeed might be detrimental, to accurate diagnosis (Kok et al., 2015). Carmody et al. (1984) also found that, although radiologists are taught to compare both lungs (to look for asymmetric findings), less than 4% of their eye movements indicated such comparison scans, further illustrating the gap between radiologic instruction and practice.

Search Patterns in Volumetric (3D) Imaging

Modern medical imaging increasingly includes not only static image viewing (e.g., mammography and plain film radiography), but also dynamic imaging, such as with sequential viewing of multiple slices of CT and MRI, often in different orientations. When reading a CT or MRI, contemporary radiologists must scroll through a stack of images-thin slices of the 3-D volume of an organ–a process known as "stack viewing" (Nakashima et al., 2016) (**Figure 2**).

Although numerous studies have examined search strategies utilized in viewing single 2-D medical images, relatively little is known about those employed during interpretation of 3-D volumetric medical images (Nakashima et al., 2016).

In many ways, stack viewing is a different perceptual task than reading static images, and it may be regarded as a type of visual search conducted in a dynamic display. During stack viewing, radiologists search for the onset signal of a suddenly appearing lesion that stands out among blood vessels and organs that appear to move (simulated motion) (Nakashima et al., 2016). Thus, the fundamental characteristics found in the search of static images do not necessarily apply to the search of dynamic displays.

Drew and colleagues identified two different global strategies adopted by radiologists when searching through volumetric images—specifically during a nodule detection task in chest CT. "Scanners" searched each slice widely, before moving on to the next depth. "Drillers" held their eyes relatively still in the x and y plane, limiting their search to a single lung quadrant while quickly scrolling—drilling—through slices in depth. The data revealed a higher true positive rate for drillers than for scanners: drillers identified 60%, and scanners identified 48%, of all available nodules (Drew et al., 2013b).

Whereas drillers had more experience than scanners in the above dataset (Drew et al., 2013b), a follow-up study showed that instruction in drilling techniques led to improved performance in residents, compared with instruction in scanning techniques (van der Gijp et al., 2017b). These combined results support the superiority of drilling vs. scanning strategies. It is also worth noting that, in contrast with of Drew et al. (2013b) findings, none of the participants in the van der Gijp et al. (2017b) study reported (or had eye movements suggestive of) 'scanning' when reading images under normal work conditions. This is consistent with one of the authors' (SW) experience.

More recently, Kelahan et al. (2018) found evidence that the 'drillers' vs. 'scanners' model is likely imperfect when applied to CT scans of the abdomen and pelvis, given there are more organs in the abdomen and pelvis than in the thorax, and radiologists looked for multiple possible imaging findings (vs. only nodules in the Drew et al., 2013b experiments). It is likely that different search techniques are used depending on imaging modality and the part of the body imaged (e.g., thoracic vs. abdominal or neurologic imaging).

In order to get a more granular understanding of scroll behavior beyond the more general concepts of drilling and scanning (Drew et al., 2013b), Venjakob and Mello-Thoms (2016) and den Boer et al. (2018) defined different types of scroll behavior during CT interpretation. Quantification of the number of slice transitions performed before radiologists change their scrolling direction can provide insight into the desired image content (Venjakob and Mello-Thoms, 2016). den Boer et al. (2018) temporally related scroll movements to cognitive data via a think-aloud strategy, whereupon radiology residents verbalized their thoughts while reading CT scans. Half runs and oscillations ('local' movements covering less than 50% of the stack slices) were often associated with analysis [defined as cognitive activities including characterization of findings (van der Gijp et al., 2014)]. Runs (movements forward or backward covering more than 50% of slices) (Venjakob and Mello-Thoms, 2016) and image manipulation (where readers changed contrast levels or stack orientation) were more frequently associated with perception—search strategies and the global search for abnormalities (den Boer et al., 2018). Interruptions (where scrolling was paused) mainly coincided with synthesis related to the integration of information (e.g., generating a differential diagnosis) (den Boer et al., 2018). It is unclear whether these findings generalize to expert search or whether the relationship between scroll behavior and cognition changes with experience, however, studies of this kind can engender further insights into how radiologists interpret volumetric examinations.

Because of the large data inherent to volumetric imaging (often 1000s of images per study) (Andriole et al., 2011), radiologists do not exhaustively foveate all regions of interest, but rely on detection of signals with their peripheral vision (Eckstein et al., 2017). Drew et al. (2013b) found that radiologists covered, on average, 69% of the lung tissue on a CT nodule detection task. In a similar nodule detection task, Rubin et al. (2015) found that observers covered, on average, only 26.7% of the lung tissue. The difference between the results from these two studies could reflect their respective operational definitions of central field size (Kundel, 2015). Yet, despite

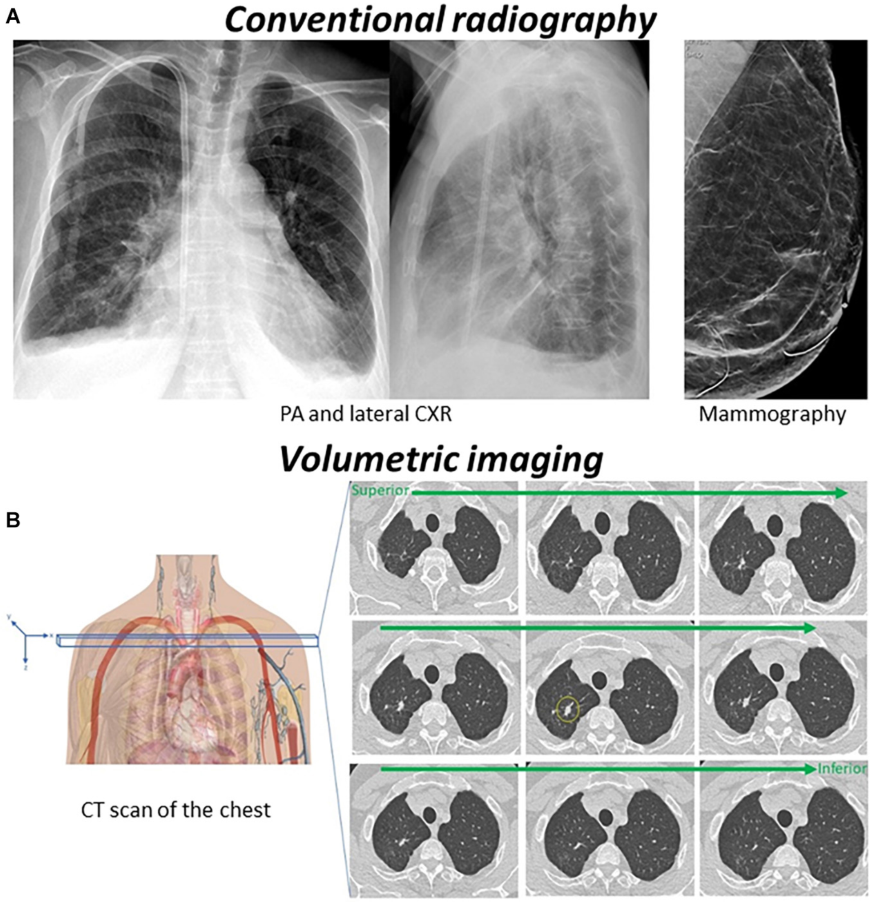

FIGURE 2 | (A) Conventional radiography (2D medical imaging) such as CXR, mammography, and plain film bone X-rays, is based on the fact that tissue will absorb photons from an X-ray beam in relation to the electron density of the tissue. The number of photons passing through the region of interest will be detected by image detectors that convert the body's direct attenuation of the photons into digital images. The resulting images are a two-dimensional projection of a three-dimensional structure. **(B)** In volumetric imaging such as CT and MRI, cross-sectional images of the body are obtained to represent a "slice" of the person being imaged, such as the slices in a loaf of bread. Once a number of successive slices are generated, they can be digitally "stacked" to form a three-dimensional image of the patient. On the CT scan above there is a nodule in the right upper lobe (yellow circle). As a radiologist scrolls through the stack, the nodule will present as a suddenly appearing (and then disappearing) lesion, simulating motion.

their discrepancies, the main common finding in both studies is that a large amount of the lung tissue is never examined with foveal vision. Interestingly, Rubin et al. (2015) found that although observers foveated less than 33% of the lung volume, their search volumes encompassed an average of 75% of all nodules, showcasing the efficiency of peripheral detection (Kundel, 2015).

As peripheral vision cannot provide the kind of fine spatial discriminations that characterizes foveal vision, detectability of certain lesions can differ in 3D vs. 2D image searches (Eckstein et al., 2017). For instance, Eckstein et al. (2017) found higher detectability for calcifications in 2D single slice images—a Gaussian noise field tuned to be similar to the noise present in mammograms, and relatively improved detection of masses in 3D volumetric imaging– a stack of 2D images where the user could scroll up and down in the stack of images in a similar manner to the way a clinician explores a digital breast tomosynthesis case (Eckstein et al., 2017).

Models of saliency further illustrate differences between 2D and 3D search, predicting that different radiologic examinations are approached in distinct ways to optimize performance. Wen et al.,(2016) made a 'dynamic saliency map' where higher saliency is ascribed to motion flows that deviate from normal dominant flows, expected to reflect the observation that nodules pop out from anatomical backgrounds during volumetric interpretation. Alternatively, the Graph-Based Visual Saliency (GBVS) model predicts saliency due to the comparison of static image features within a given slice. Wen and colleagues demonstrated that driller fixations were aligned better with the dynamic saliency map and scanners with GBVS. This suggests that topographic maps representing conspicuity of objects and locations differ between radiological viewing methods, and more specifically, that scanners tend to use primarily 2-D information in their search, whereas drillers (the great majority of radiologists) use more dynamic information when interpreting cross-sectional imaging (Wen et al., 2016).

Both Wen's and Eckstein's studies lend support to the notion that 2D search and volumetric search are different perceptual tasks, and thus observer performance in one may not generalize to the other (Wen et al., 2016; Eckstein et al., 2017).

Search Patterns and Spatial Frequency Analysis

The ability to detect a lesion is not only dependent on lesion characteristics, but also on the relation between the lesion and the background. As described in the holistic model of medical image perception, a target is compared to its background (which may camouflage the target, causing recognition error) to determine whether it is noteworthy (Nodine and Kundel, 1987). The relation between the lesion and the background therefore determines whether any given lesion will be above or below the detection threshold for a given decision criterion (Mello-Thoms et al., 2003). Mello-Thoms (2003, 2006), Mello-Thoms et al. (2003), and Mello-Thoms and Chapman (2004) performed a number of studies using image processing in order to understand the interplay between lesions and the parenchyma during mammographic interpretation. Using wavelet packet decomposition, they measured the log of the energy (energy being the integral of the signal strength) of different spatial frequency bands across a range of orientations and made a profile of measurements for each fixated region (Mello-Thoms, 2003). Because radiologists make comparative judgments between the background and any potential lesions, Mello-Thoms et al. (2003) considered not just the profile in each region (termed the local profile) but also a combined profile (the global profile) across all fixated regions in an image. The local profile is related to the conspicuity of local features and the global profile is a measure, specific to each observer, of the searched background to which local features are compared (Taylor, 2007).

Both residents and mammographers were visually attracted to similar areas of mammograms, despite mammographers having significantly superior accuracy (Mello-Thoms et al., 2003). The data showed that the computed profiles did not discriminate between mammographers' true- and false-positive decisions, suggesting that they possess mental schema (well-modeled by the spatial frequency representation) about how malignant lesions should look, and they do not deviate from that schema even when they make a mistake (a false positive). The profiles did, however, discriminate between mammographer's true-positive and false-negative decision outcomes. For residents, however, there were statistical differences between false and true positives, and the global profile seemed to play a much smaller role in their decision-making, implying that conspicuity of local elements is strongly related to their decisions. Residents were less able to contrast local findings with global features, which misguided their judgments (Mello-Thoms, 2003; Mello-Thoms et al., 2003). Further understanding of what imaging features attract visual attention in conjunction with decision making can afford more specific training- for example by concentrating on residents' improving their comparison skills during training (Mello-Thoms, 2003).

CHALLENGES TO EYE TRACKING STUDIES

Simple eye movement measurements may only provide meaningful data on radiologic expertise in certain imaging scenarios (Jarodzka and Boshuizen, 2017). For example, time to first fixation and the proportion of time spent on relevant findings, is only informative in the case of localized diseases, but not for diseases that are diffuse in nature (and may thus require more complex metrics) (Kok, 2012).

Kok (2012) found that radiologists examine diffuse and focal diseases on chest X-rays differently. In addition to 'standard' eye tracking measures they examined the 'global/local ratio' of saccades—computed by dividing the number of 'long' by 'short' saccades (respectively defined as greater and less than 1.6 degrees of visual angle). A higher ratio indicated a global, dispersed viewing pattern, and a lower ratio indicated local clusters of fixations in specific regions (Kok, 2012). Although there were significant differences in interpretation accuracy (determining the *likely* diagnosis for the examination) between attending radiologists and medical students (no difference was found in accuracy between residents and attendings), the global/local ratio between groups was similar in diseased images. The fact that all groups changed their viewing pattern according to the type of disease, but that medical students had significantly worse interpretation accuracy, is evidence that perceptual aspects of image interpretation- *detecting* abnormalities- develop before the ability to correctly interpret abnormalities or integrate them into a correct diagnosis (Kok, 2012). Further studies with more complex oculomotor metrics will be needed to unravel the relationship between eye movements and diagnostic expertise.

A recent study by Kasprowski et al. (2018) challenges the presumed relationship between visual search efficiency and diagnostic accuracy. They analyzed various eye movement metrics while four participant groups viewed CXRs preceded by proposed answers: observers with no medical experience, radiology technicians ('radiographers'- skilled in performing X-ray examinations but not involved in diagnosis), radiology residents, and radiology attendings. As expected, attendings had the highest average diagnostic accuracy, followed by residents, radiographers, and laypeople. Interestingly, although there were significant differences in the eye movement metrics of residents and attendings, there were no significant differences between the visual patterns of radiology *technicians* and attendings, despite residents being significantly more accurate. The authors surmise that this finding may reflect general experience analyzing X-rays. Their participant radiographers had over 10 years' experience checking the *technical* quality of imaging, compared to participant residents, who had less than 6 years' experience, albeit for a different purpose—diagnosis. Thus, the ability to reproduce characteristics of experts eye movements does not guarantee improved diagnostic performance (Kasprowski et al., 2018). Expertise in radiology requires not only efficient, task-oriented, eye movements but accurate recognition of abnormalities.

An additional confound is that eye tracking metrics are not only dependent on imaging findings and reader expertise, but are also influenced by clinical history (reviewed in Waite et al., 2017b) and reader expectations of abnormal findings. In an analysis of 16 studies comparing the accuracy of tests with and without clinical information, Loy and Irwig found that clinical information improves interpretive accuracy through improved sensitivity without a loss of specificity, consistent with readers being alerted to additional imaging features, rather than by merely altering their level of suspicion (Loy and Irwig, 2004). Although many of these studies were not performed with associated eye tracking metrics, search patterns likely also vary in conjunction with changes in accuracy. Moreover prevalence expectation changes search patterns. Reed and colleagues studied performance during a CXR-based nodule detection task under conditions where readers were told that the images contained a specific number of abnormal findings. Higher prevalence expectations were linked to increased reader fixations and total analysis time (Reed et al., 2011). A follow-up study demonstrated that this ‘prevalence effect’ was particularly evident in normal examinations, with readers exhibiting decreased confidence that normal images were in fact normal (Reed et al., 2014).

A more fundamental challenge to assessing the findings of many eye tracking studies’ relates to their experimental design. Gur et al. (2008) and Gur (2009) found that radiologic performance during the interpretation of mammograms was different in real-life vs. laboratory settings.

Lastly, Van der Gijp and colleagues noted that studies conducted over the last two decades have largely focused on the differences between experts and novices, while theory-driven research on how to improve detection has been relatively neglected. Thus, there is a need for the field to move beyond the description of differences between experts and novices, to the development of more efficient strategies and methods to accelerate and improve training (van der Gijp et al., 2017a).

HOLISTIC ‘GIST’ PROCESSING THEORY

Prevailing models of medical image perception rest on the premise that expert observers process a medical image holistically at the first glimpse. These holistic processing accounts are encompassed by a couple of different theoretical frameworks, the oldest described being the global-focal search or ‘holistic’ model (Nodine and Kundel, 1987; Litchfield and Donovan, 2016; Sheridan and Reingold, 2017).

According to the global-focal search model, medical experts rapidly extract a global impression of an image. This impression consists of a comparison between the contents of the image and the expert’s prior knowledge about the appearance of normal and abnormal medical images (i.e., the expert’s schemata). This enables experts to identify perturbations (deviations from their schemata that indicate possible abnormalities) and direct their eyes toward their corresponding locations for further (i.e., foveal) examination (Nodine and Kundel, 1987; Sheridan and Reingold, 2017). Features are subsequently scrutinized and tested against schemata to determine whether a finding is suspicious, in which case diagnostic decisions are made (Waite et al., 2017b) (for a more complete review see, Kundel et al., 2008). This process, lasting seconds to minutes, is capacity-limited by the bottleneck of attention (Waite et al., 2017b). Similar time constraints apply to all models that rely on global processing as a core component of expertise in medical image perception (Sheridan and Reingold, 2017). Another popular model posits that initial global processing (consisting of bottom–up “global image statistics” like average orientation and average size of objects) signals if there is an abnormality (establishing its likelihood) without providing *location* information or constraining the subsequent serial search. The searcher can then change their strategy to a slower, more complete search for the abnormality (Evans et al., 2010, 2016; Drew et al., 2013a; Chin et al., 2018) (**Figure 3**).

One of the global-focal model’s principal predictions is that rapid initial global processing constrains search to suspicious areas in the image (Carrigan et al., 2018). This strategy may be available to experts but not novices, explaining why expert observers search medical images with higher efficiency—finding more abnormalities in a shorter timeframe, and with fewer eye movements—than novices do. Support for this hypothesis has been provided by studies showing that expert radiologists can identify subtle abnormalities on mammography and chest radiography displayed for only 250 ms (Kundel and Nodine, 1975; Oestmann et al., 1988; Krupinski, 2011; Evans et al., 2013; Sheridan and Reingold, 2017; Carrigan et al., 2018).

Using time to first fixation on lesion data during mammographic interpretation, Kundel and colleagues found that 67% of cancers were fixated on within the 1st second of viewing. The remainder of the cancer locations were fixated on later in search. This has been interpreted as further supporting a two-component system- rapid initial holistic processing guides initial search with subsequent slower processing representing discovery of cancers from search and discovery (Kundel et al., 2008).

The idea that holistic processing is integral to expert performance is also supported by experiments designed to disrupt it. Oestmann et al. (1993) found decreased detection performance for subtle lung cancers in upside-down images, even with unlimited viewing times. In a related study, Carmody et al. (1980) compared nodule detection performance in two viewing conditions: *segmented search*—in which the CXR was presented in six sections and viewed piecemeal—versus *global search*—in which the entire film was presented—and found an increased false positive rate in the segmented search scenario, which they attributed to an impaired gestalt.

Face perception is considered a prime example of holistic processing, where recognition is based on the synthesis of facial features that yields a unique face more than the summed recognition of each individual facial feature. The ‘gold standard’ for testing holistic face processes is the face inversion task, whereupon inversion *disproportionately* impairs the recognition of faces relative to other object classes. Turning a face upside down is thought to disrupt normal holistic face processing, forcing participants to use a less optimal strategy based on analysis of specific features (e.g., wide-set eyes, square jaw). Processing in mammographic interpretation appears to share similar characteristics to this holistic perception. In a recent

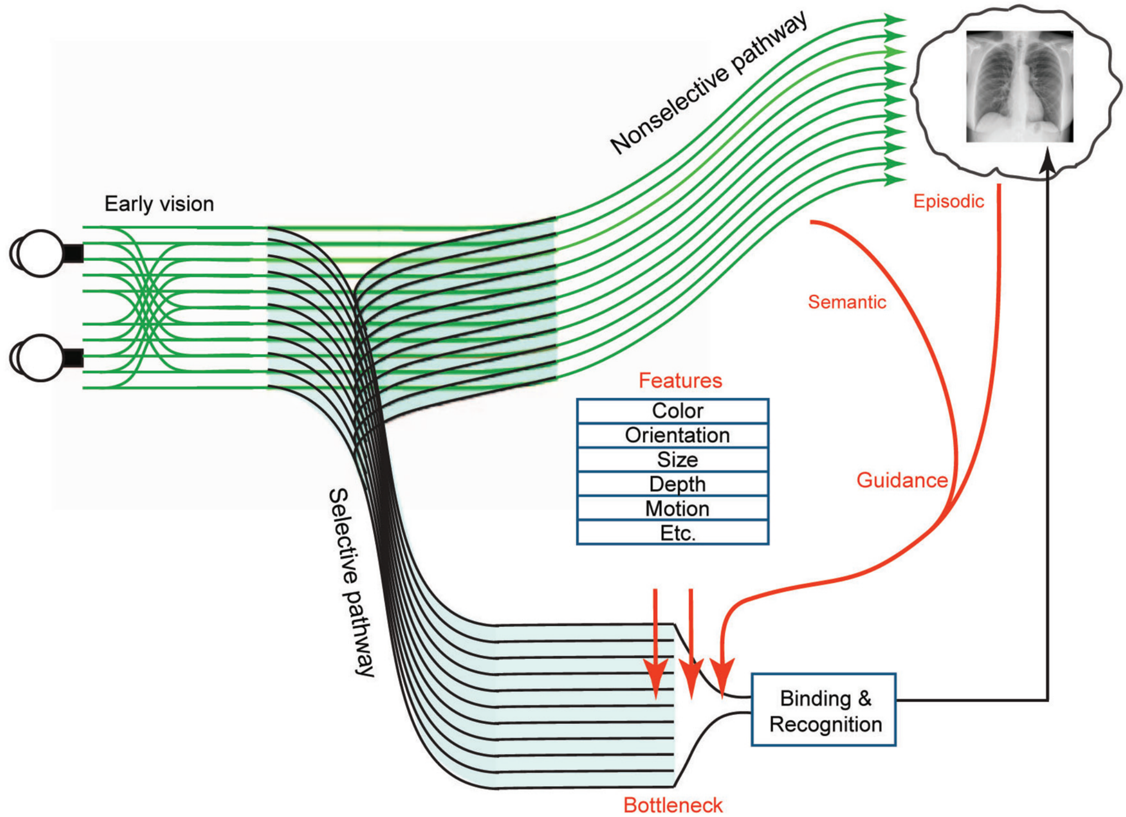

FIGURE 3 | Figure modified from Wolfe et al. (2011) with permission. Two-pathway architecture for visual processing. The selective pathway can bind features and recognize objects but is capacity-limited. At its bottleneck, preference for further processing is given to items with certain basic attributes (such as color, orientation, and size) when those attributes match the appearance of a target object. However, these attributes do not fully explain the efficiency of search in the real world, where elements are arranged in a rule-governed manner—for example, people generally appear on horizontal surfaces. The regularity of scenes provides two kinds of scene-based guidance—semantic guidance, referring to the knowledge of the probability of the presence of an object in a scene and its probable location, and episodic guidance, referring to the memory of a *specific* previously encountered scene. In conjunction with the selective pathway, the non-selective pathway extracts statistics such as velocity, direction of motion, and size, rapidly from the entire image. Although the non-selective pathway does not support precise object recognition, it provides information used in scene-based guidance to direct attention to important locations (such as the probable locations of nodules on CXR's). Conscious experience of the visual world is comprised of the products of both pathways (Wolfe et al., 2011).

study, Chin et al. (2018) tested the effects of image inversion during interpretation of normal and abnormal mammograms-inverted and normally oriented-by experienced radiologists and radiology residents (**Figure 4**). Participants were also asked to judge the facial expressions (e.g., neutral/happy) of briefly presented upright and inverted faces (Chin et al., 2018). Both groups demonstrated better expression discrimination of faces in the upright compared to the inverted orientations, as expected. However, detection rates for upright and inverted mammograms depended on expertise level. Whereas radiology residents were unaffected by image orientation, experienced radiologists performed better on upright images than on inverted ones. In addition, although accuracy in the upright position increased with years of experience, the magnitude of the inversion effect *also* increased, demonstrating that use of holistic strategies increases as a function of domain-specific perceptual experience. In short, expert holistic processing helped in detection of an upright stimulus but provided no advantage when the image was inverted (Chin et al., 2018).

A recent study by Brennan et al. (2018) suggests an intriguing relationship between expertise and gist processing. They found that not only could radiologists detect cancer above chance in abnormal mammograms viewed for only 1/2 second, but they were able to differentiate between normal mammograms in patients that *remained cancer free after 2 years* from normal mammograms in patients that subsequently developed cancer. These results suggests that mammograms without overt signs of cancer can contain information that may predict future malignancy. The readers that most rapidly differentiated between positive and negative mammograms were also better at differentiating between normal mammograms in patients that remained cancer free and normal mammograms in patients where cancer developed later. Their results suggest that expertise may increase radiologists' capacity to perceive the 'gist of the abnormal,' an ability to detect a globally elevated risk of cancer in studies without overt radiographic signs (Brennan et al., 2018).

In a related experiment, Evans and colleagues found that expert mammographers demonstrated above-chance

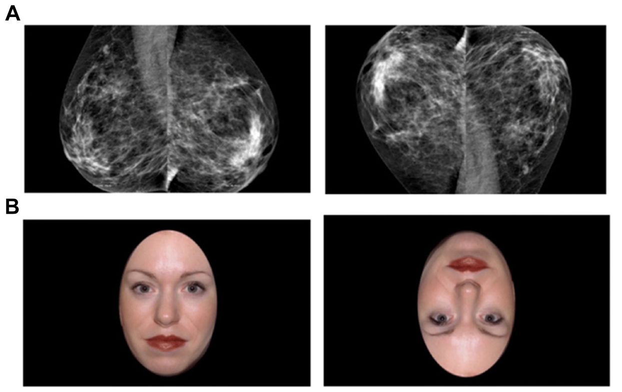

FIGURE 4 | Reprinted from Chin et al. (2018) with permission. Examples of mammogram and face stimuli in upright and inverted orientations. **(A)** Upright and inverted abnormal mammogram. **(B)** Upright and inverted smiling face. The inversion effect posits that stimuli are processed as an integrated whole rather than a sum of its parts; therefore, the inverted image is harder to recognize and process (Chin et al., 2018).

classification of a study as abnormal when shown 500 ms images from the *normal breast* in patients with overt signs of cancer in the *opposite breast*. This suggests that a widely distributed 'global signal of abnormality' was present in the normal breast parenchyma (Evans et al., 2016). Evans et al. proposed that such a signal, if present before the appearance of a clinical lesion, could be used as a warning sign suggesting greater vigilance (Evans et al., 2016). One possible way to accomplish this would be to flash an image for a half-second, record the readers' gist response *before* usual presentation, and then use this signal to predict future breast cancer (Brennan et al., 2018). In conjunction, given a high gist response correlates with cancer in the *current* image, it might be cost-effective to send an image to a second reader for double reading when a case is classified as abnormal from the gist response, but reported as *normal* after usual presentation (Brennan et al., 2018).

CHALLENGES TO HOLISTIC PROCESSING THEORY

Volumetric Imaging

Holistic processing theory is at best incomplete as a model of perceptual expertise in the era of modern imaging. The studies that buttressed the holistic processing model were conducted with plain 2-D imaging such as CXR (Kundel and Nodine, 1975; Oestmann et al., 1988) and mammography (Evans et al., 2013), but the nature of 3D volumetric imaging (with the necessity to scroll through images in the z-plane to detect abnormalities) is such that no single image can provide meaningful global image statistics or afford knowledge of image perturbations throughout the entire dataset. Therefore, there is no rapid 'global signal' that can be extracted from any single image to either organize subsequent fixations or contribute to the reader's conviction that a subsequent search will uncover an abnormality.

Flash Preview Moving Window (FPMW) Experiments

One of the problems with assessing the validity of the holistic model in radiology is that the corresponding studies were conducted under free-viewing conditions. Because observers had constant access to the whole scene via peripheral vision, it is difficult to isolate the specific contribution of the initial scene preview on subsequent eye movement behavior (Litchfield and Donovan, 2016).

The flash preview moving window (FPMW) protocol draws from both 'flash' methodology and a 'moving window' paradigm. A brief preview of a scene is shown to observers, who must then search for a target within the scene while their peripheral vision is restricted (Litchfield and Donovan, 2016). To control how much of the scene is accessible for visual processing, a mask of variable size is tied to the observer's central fixation, occluding the rest of the scene outside the fixation window. In this way, observers remain free to make eye movements, while researchers systematically control how much foveal, parafoveal, and peripheral information is available for visual processing. As a result, observers may examine a scene solely with high-resolution foveal vision, isolated from parafoveal or peripheral contributions (Litchfield and Donovan, 2017) (**Figure 5**).

Using this protocol, Litchfield and colleagues found that, whereas experts (consultant radiologists) identified more nodules on CXR than novices (psychology undergraduates), denying experts an initial glimpse of the image did not impact their performance. In contrast, novices performed better in the *mask* preview condition than with the scene preview. Further, the first eye movements following the scene preview and the mask preview had comparable speeds and amplitudes (Litchfield and Donovan, 2016). Thus, contrary to predictions from the holistic processing theory, the provision of an initial glimpse of the scene did not contribute to expert performance—and indeed *reduced* novice performance.

A follow-up experiment compared the detection performance of novices and experienced radiographers in three different imaging modalities—CT scan of the head, skeletal x-rays, and CXRs—for specific target abnormalities. As expected, the detection skills of experienced radiographers surpassed those of novices. However, access to a scene preview not only did not benefit, but actually *impaired* the performance of observers in both groups (Litchfield and Donovan, 2016). These combined findings argue against the hypothesis that processing the initial glimpse of a scene is beneficial to performance (Litchfield and Donovan, 2017) (but see Sheridan and Reingold, 2017 for a counterpoint).

Scene Processing Without Attention?

We also note that flash preview experiments (Kundel and Nodine, 1975; Krupinski, 2011; Evans et al., 2013) are thought to support the holistic processing hypothesis based on the assumption that searchers only use information available *while* images are displayed (Sheridan and Reingold, 2017). Yet, there is reason to believe that image processing can continue *after* images are no

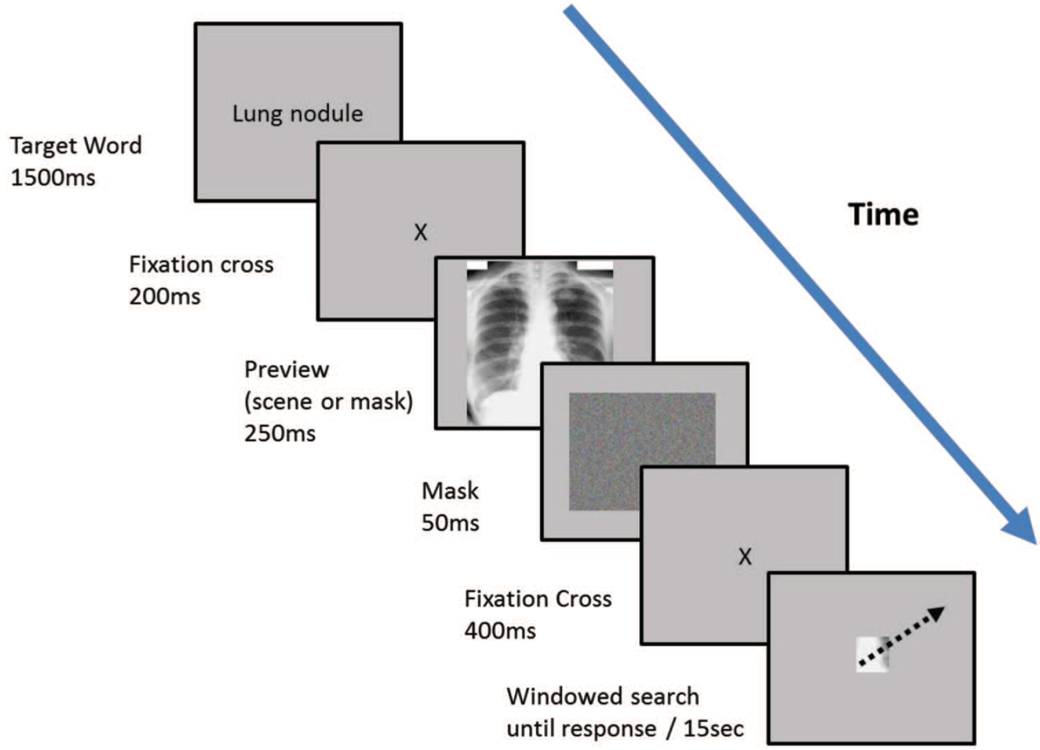

FIGURE 5 | Reprinted from Litchfield and Donovan (2016) with permission. Two different experience groups—expert radiologists and psychology students—searched for lung nodules from CXR images using the flash-preview moving window (FPMW) paradigm. Participants looked at the target word for 15 s ("lung nodule"). They then saw a fixation cross for 200 ms, then either a mask preview (random array of colored pixels) or a CXR (a 'scene' preview) for 250 ms. Next, participants saw a mask for 50 ms and then a second fixation cross for 400 ms. Following a second presentation of the fixation cross, they conducted a windowed search, with a 2.5-degree radius window restricting the field of view (Litchfield and Donovan, 2016).

longer displayed, even in the presence of a mask (Carrasco and McElree, 2001; Carrasco et al., 2003).

More generally, gist processing is thought of as a type of scene processing that occurs in the absence or near absence of attention (Li et al., 2002; Rousselet et al., 2002; Fei-Fei et al., 2005; Otsuka and Kawaguchi, 2007), in parallel across the visual field (Rousselet et al., 2002). But even if the initial glimpse of a scene is demonstrably helpful, it does not necessarily follow that searchers process information without attention. Instead, it may be that searchers rapidly extract visual information during a single brief fixation that provides high-resolution information at the fovea, and lower-resolution information in the visual periphery (Livingstone and Hubel, 1988; Strasburger et al., 2011), facilitated by attention. Attentional allocation to the periphery might involve one or more serial shifts of selective processing, either covertly during the first fixation or while continuing to process the image in memory, before the observer is required to provide a response. Carrasco et al. (2003, 2004, 2006) showed that peripheral stimuli continues to be processed after being removed from view, with the temporal dynamics depending on where stimuli are in the visual field, within the timeframe allowed by many gist experiments. Either scenario would be contrary to the concept of gist as occurring merely in parallel across the visual field and in the absence or near absence of attention.

THE DEVELOPMENT OF PERCEPTUAL EXPERTISE IN RADIOLOGY

Kelly and colleagues found that certain ocular metrics (such as time to first fixation) improved at an earlier stage of training than diagnostic accuracy in pneumothorax detection. This same study found significant differences in diagnostic accuracy, but not in the ocular metrics, of consultants (equivalent USA rank: attending) vs. registrars (equivalent USA rank: fellow), suggesting that expert gaze dynamics are learned at a faster pace than diagnostic abilities, and that they plateau at a relatively early stage of formal residency training (Kelly et al., 2016).

Ravesloot et al. (2017) found that scores from image interpretation questions (image-based questions testing interpretation skills) improved faster than knowledge-based questions (text-based factual questions) for the first 3 years of residency when residents took the Dutch Radiology Progress Test, a mandatory semiannual test taken by all Dutch radiology residents (**Figure 6**).

Both eye tracking metrics and performance on image interpretation-based questions show that the ability to analyze images develops at a faster rate than factual knowledge. Whereas radiologists' perceptual skills begins to grow from the start of exposure to imaging, radiology-specific factual

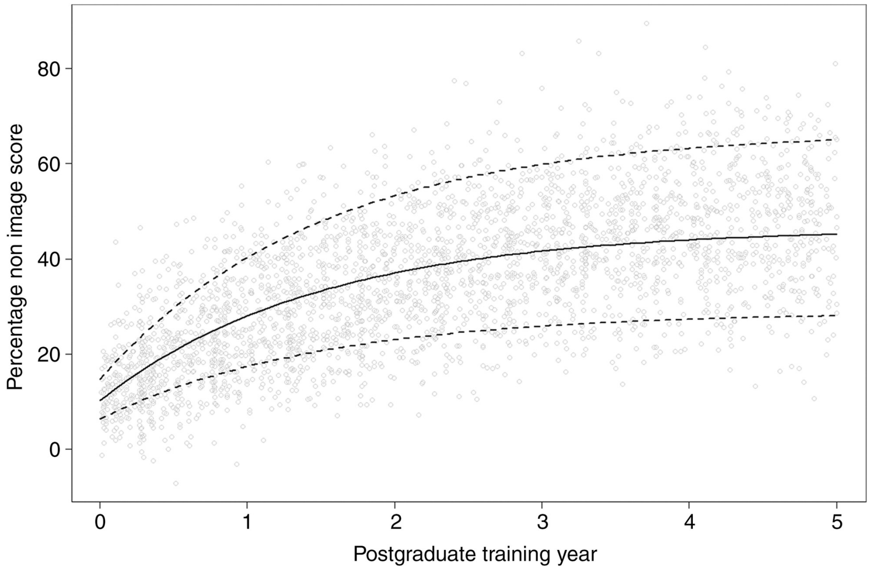

FIGURE 6 | Reprinted from Ravesloot et al. (2017) with permission. Graph estimating image interpretation skill development during residency, as measured by the Dutch Radiology Progress test. Image score measures performance on image interpretation skills as opposed to factual knowledge. The score represents percentage from the maximum possible score and is calculated by subtracting the number of incorrect answers from the number of correct answers to account for guessing (making a negative value possible). The slope represents the speed of skill development and measures 16.8% during the first year of training. The slope decreases by 50% every year until it reaches 2.0% at the end of training. Note that the maximum image-score is estimated at 55.8%. Dotted lines represent the middle 95% of performances (Ravesloot et al., 2017).

knowledge contributes little to this initial development (Ravesloot et al., 2017).

Together, these studies also indicate that perceptual expertise plateaus early with a high level of error. Worse, this plateau likely persists beyond a radiologists formal training period, an important issue for residency programs to address.

CHALLENGES TO THE FUNCTIONAL DEFINITION OF EXPERTISE

The functional definition of expertise in the literature is limited for a number of reasons. Radiologic learners are often classified into the broad categories of experts versus novices, dramatically oversimplifying reality while disregarding intermediate training stages (Gunderman et al., 2001). Even studies that include intermediate stages in their analyses base their categorization on the *professional* level of training (Kundel et al., 2007). Indeed, a large meta-analysis of eye tracking research in professional domains found that in 6 of 8 radiology-based studies, expertise was determined solely according to professional levels of training and/or years of experience (Gegenfurtner et al., 2011). Fox and Faulkner-Jones (2017) note that experimental designs tend to include at most three participants groups, and bin medical students as novices, radiology residents as intermediate-level trainees, and attendings as experts.

The assignment of the ‘expert' label purely based on professional degrees, rank, or experience is problematic for reasons both theoretical and practical. Although a specific attending may be considered to be an ‘expert' by peers because of an extensive knowledge base, this does not necessarily directly translate into perceptual expertise. As Gunderman notes, expertise in one radiologic domain does not necessarily apply to every domain (Gunderman et al., 2001). For instance, Beam et al. (2006) and Elmore et al. (2016) note that mammographers have two distinct tasks: (1) Interpretation of screening mammograms and (2) Interpretation of abnormal screening mammographic findings. The first task requires evaluation of standard images from a large population of individuals without specific signs or symptoms (considered ‘perceptual'), whereas the second task requires careful analysis of specific abnormalities (considered more ‘cognitive') (Beam et al., 2006; Elmore et al., 2016). Both studies found only a *moderate* correlation between radiologists' performance in the two domains. In other words, proficiency in one area did not guarantee proficiency in the other (Beam et al., 2006; Elmore et al., 2016). The presence of wide disparities in screening and diagnostic interpretive skills in the same individual has been described as ‘expertise disequilibrium' (Beam et al., 2006). In addition, assuming perceptual expertise based purely on experience negates any potential effects from age-related declines in contrast sensitivity, known to be most marked for high spatial frequencies (Owsley and Burton, 1991; Davies et al., 1994).

It follows that, even if attendings are considered ‘experts' by their peers (or by rank or by years of training), they are not *all* de-facto *perceptual* experts and indeed may be highly capable in only a subclass of the complete radiology skillset. This heterogeneity is problematic if, in fact, homogeneity of expertise is assumed when evaluating radiologists' perceptual performance (i.e., such as in a nodule detection task study).

Bearing out these theoretical concerns, several research studies have demonstrated that residents in the 'intermediate bin' can outperform 'expert' attendings. Rubin et al. (2015) found no significant correlation between experience and detection of artificially placed nodules in CT examinations. Indeed, at least one resident in their *first* year of training outperformed a *sub-specialist thoracic radiologist* in their specialty, despite an extensive experience differential (Rubin et al., 2015). Similarly, Kelly et al. (2016) found that less experienced radiologists occasionally outperformed more experienced radiologists in pneumothorax detection. Kundel et al. (2007) found a wide range of diagnostic performance across residents, fellows, and attendings when looking at a test set of mammograms. Hanna et al. (2018) likewise found that residents could outperform attendings in a fracture detection task under both fatigued and non-fatigued conditions. Lesgold et al. (1988) discovered that more advanced residents were occasionally less likely to make a correct interpretation on several complex x-rays compared to more junior residents. Finally, Nakashima et al. (2016) found no difference in performance in a nodule and bullae detection task on CT amongst radiologists with experience ranging from 3 to 15 years.

In summary, experience is a necessary, but insufficient, indicator of expert performance (van der Gijp et al., 2017a). At best, experience is an uncertain predictor of expertise level, and at worse, it reflects little more than seniority (Shanteau et al., 2002). Likewise, the use of certification (such as conferred from the American Board of Radiology) as a marker of expertise is limited in that it is most often tied to years on the job, rather than to objective performance. To compound the problem, certification suffers from the 'ratchet up effect,' whereupon individuals move up but not down the ladder, even if their skill level suffers a serious decline over time (Shanteau et al., 2002). Ericsson has noted that there is little empirical evidence for the traditional view that expertise is acquired through extended experience alone (Ericsson, 2004). Instead, the development of expertise more likely arises from domain-specific 'deliberate practice,' with accurate and detailed immediate feedback and opportunities for repetition (Causer et al., 2014; Ericsson, 2017). It follows that if a first year resident outperforms a fellowship-trained thoracic radiologist in nodule detection, the resident should be labeled as an 'expert' (in studies of *search* tasks), irrespective of their lack of experience. Defining expertise by performance, rather than by titles, is therefore liable to produce more accurate data.

A WAY FORWARD—WAYS TO PROMOTE PERCEPTUAL EXPERTISE

The Role of Subspecialty Training

Given increasing specialization in medicine, some authors have advocated that radiology groups pursue a subspecialization model (Strax, 2012; Gunderman and Stevens, 2014; Arenson, 2018). Indeed, several studies have shown that subspecialists have better accuracy in their relative subfields than general radiologists (Sickles et al., 2002; Briggs et al., 2008; Bell and Patel, 2014; Kligerman et al., 2018), perhaps due to limiting the field of scope and enhanced networking with subspecialty medical experts whom provide prompt feedback. Thus, concentration on a narrow field may be a way to achieve the case volume and feedback needed to ensure expertise.

Perceptual Learning

Perceptual learning may be defined as "an increase in the ability to extract information from the environment, as a result of experience and practice with stimulation coming from it" (Gibson, 1969). In general terms, this refers to how experience can change the way we perceive sights, sounds, smells, tastes, and touch. Such continuous learning is the foundation of perceptual competence and eventual expertise. As such, it is a topic of intense and increasing scientific study. For recent reviews see (Lu et al., 2011; Gilbert and Li, 2012; Sasaki et al., 2012; Kawato et al., 2014; Li, 2016; Seitz, 2017).

The developing brain calibrates its perceptual systems through interaction with the environment; for instance, tuning and updating neural representations of our body and sensory organs as we grow (i.e., the length of our limbs changes with age). Much of this learning occurs during critical periods in early infancy, when the brain is most plastic, and its processes and connections are easily molded by experience. It is during such critical periods that changes in visual experience can have profound impact on the functional organization of the brain regions underlying perception. Yet, even though neural plasticity is diminished in adults, it is not lost. Indeed, with proper training, adults can exhibit an impressive degree of perceptual learning. A variety of stimuli including texture, orientation, contrast, and motion are used in visual perceptual learning research (**Figure 7**).

Perceptual learning studies most often focus on a specific visual feature, such as orientation, and train participants with exemplars. Typically, performance thresholds improve over time, so that by the end of training participants can accurately discriminate stimuli that would have been indistinguishable to them at the study's onset. This type of learning differs from more conventional instruction methods where training is understood as consisting of facts, concepts, and procedures that are stored in one's mind and later retrieve as needed for

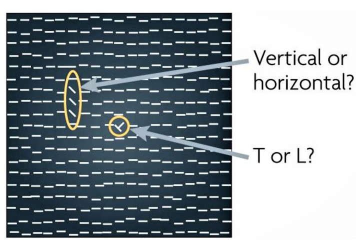

FIGURE 7 | Reprinted from Sasaki et al. (2010) with permission. Texture-discrimination tasks such as depicted here are frequently used in visual perceptual learning (VPL) studies. The subject is first asked to report whether a 'T' (as in this example) or an 'L' is presented in the center of the display to ensure fixation, and then whether the orientation of the target (which is comprised of the three elements with orientations that depart from those of the other elements in the display) is vertical (as in this example) or horizontal. VPL of the target orientation is examined.

performance. This "container" model of the mind has come into question, however, in light of persistent problems in learning and instruction (Kellman, 2013). Students who have been faithfully taught and diligently absorbed declarative and procedural inputs occasionally fail to recognize key structures and patterns in real-world tasks. In addition, they may know how to perform procedures but fail to understand their application, especially to new problems or situations. Lastly, learners may understand concepts but process them slowly, with a high cognitive load, which leads to impairment in demanding, complex, or time-limited tasks (Kellman, 2013). One of us (SW) has encountered medical students who, after reviewing basic CXR principles from textbooks for a month, did not know how to apply their declarative knowledge in any practical sense, to interpret novel examinations. In other words, students may be able to memorize isolated, inert facts, but lack the ability to use them constructively to solve problems in radiologic diagnosis (Gunderman et al., 2001).

Whereas novice trainees tend to engage in more feature-based 'analytical' processes, experts perform more rapid pattern recognition, which relies in part on experience-based perceptual (a form of 'implicit') learning (Rimoin et al., 2015). Two broad categories of perceptual learning effects have been described: discovery and fluency (Kellman et al., 2008; Kellman, 2013). Discovery effects involve finding information relevant to classifications, extracting it selectively and distinguishing important structures from irrelevant variations. Fluency effects involve improvements in the extraction and encoding of relevant information. Effects include speed, parallel processing, and automaticity (experts demonstrate lower cognitive load than novices), allowing efficient perceptual classification to coexist with other cognitive processes in complex tasks (Krasne et al., 2013).

One of the major problems in radiology education is the lack of formalization and verbalization of what exactly happens during visual information extraction (i.e., "How do you teach to *see* a nodule?") (Kellman and Garrigan, 2009; Krasne et al., 2013). Instead, it is assumed that advanced pattern recognition and automaticity will eventually arise from long apprenticeships, leaving crucial aspects of learning to occur in an unsystematic fashion, over an unspecified time, with unquantified results (Krasne et al., 2013).

Perceptual training, aimed at developing *perceptual* skills, has been applied to domains of human activity ranging from cricket play to language learning to airplane navigation (Tallal et al., 1996; Hopwood et al., 2011; Kellman and Kaiser, 2016). In the case of visual-based medical specialties, such as pathology, dermatology, and radiology, perceptual learning may be used to teach trainees how to visually recognize abnormalities, rather than how to interpret medical imaging based on a formal set of explicit rules (Chen et al., 2017). Yet, although this learning is a ubiquitous process in the adult brain, its implementation can require 10s of 1000s of trials of practice—without the certainty of learning success. Mere exposure to visual stimuli can produce perceptual learning, but it is often insufficient to yield robust results in the absence of additional factors, such as attention and reinforcement (Seitz, 2017).

Perceptual learning can be aided by training with attention. Covert attention, our ability to selectively process information at a given location without directing our gaze to that location, improves performance in many visual tasks mediated by basic visual dimensions, e.g., contrast sensitivity, spatial resolution and orientation (for reviews see Carrasco, 2011; Anton-Erxleben and Carrasco, 2013; Carrasco and Barbot, 2014). Research from the Carrasco lab has shown that covert attention can enable learning, in situations in which learning does not occur with training for the same time without attention (Szpiro and Carrasco, 2015), and facilitates transfer of learning to untrained locations (Donovan et al., 2015; Donovan and Carrasco, 2018). Possibly accounted for by plasticity in intermediate perceptual and higher decision-making brain regions, perceptual learning likely involves changes across a distributed collection of cortical areas (for review, Maniglia and Seitz, 2018). Although much of the research thus far has focused on low level perceptual discriminations, there is considerable evidence that perceptual learning is equally applicable to high-level, complex tasks (Kellman, 2013; Krasne et al., 2013).

Kellman and colleagues combined perceptual learning and adaptive learning methods (training that adapts in real-time to the trainees' activity, and adjusts to their performance) to develop a web-based instruction program dubbed Perceptual and Adaptive Learning Modules (PALM), which does not rely on explicit instructions (Kellman et al., 2008; Rimoin et al., 2015). The PALM database includes multiple categories of diseases, and a typical module presents the learner with the task of discriminating or classifying a structure over a variety of instances, allowing the learner to discover the invariant properties of the given structure (Kellman et al., 2010). Mastery is gauged based on both accuracy and response time, given that experts are not only more accurate, but also able to complete tasks in a shorter time (and with less cognitive effort) than novices (Gunderman et al., 2001).

PALM has been successfully applied in medical perceptual training, including teaching histopathologic and dermatologic diagnosis to medical students, and echocardiography interpretation to anesthesiology residents. Learners demonstrated improvements in accuracy and fluency (sequential accurate responses made with short response times) even 6 months after training. Their training gains surpassed those typically obtained in traditional teaching (Krasne et al., 2013; Rimoin et al., 2015; Romito et al., 2016).

Sowden et al. (2000) conducted one of the first perceptual learning studies in radiologic imaging. They found that novice film readers improved their discriminations of clusters of microcalcifications in mammograms, and reduced their decision speeds, after following a perceptual learning regime where they viewed 60 images, three times each day, for 4 days. Negative feedback was provided in the form of a computer beep when the wrong cluster location was selected (Sowden et al., 2000). Remarkably, this work showed that, whereas radiologists in training may have already seen 1000s of images, even small amounts of practice in a relatively short interval, can produce significant improvements in sensitivity (Sowden et al., 2000; Krasne et al., 2013).

Chen et al. (2017) examined the efficacy of perceptual learning on the performance of novices with no prior knowledge of plain film interpretation, on the detection of hip fractures. They found that top performing novices achieved comparable accuracy to that of board-certified radiologists after 1280 images and 52 min of training. Whereas it is not known to what degree these findings might extrapolate to different pathology or imaging modalities, the data speaks to the potential of perceptual learning in radiology training (Chen et al., 2017) (**Figure 8**).

Books and digital resources abound to generate differential diagnoses for problematic findings (with pictures of representative abnormalities), but none of these resources address the first step of interpretation: perception. The fact that observational errors constitute the bulk of interpretive error in radiology (and that error rates have not changed in over half a century) (Waite et al., 2017b), highlights the need for (a) new educational methods to teach radiologists in training, and (b) the reassessment of present didactic and question-and-answer instruction techniques.

A NEW RESEARCH PARADIGM

As outlined in this review, there have been important strides in understanding the nature of a radiologists' perceptual expertise. In short, experts possess more refined and complex search strategies, organize information more efficiently (Lesgold et al., 1988), are faster and in general make less perceptual errors than novices, partially because they are better able to discern lesions from the background. Yet, there is no concrete evidence that radiologists have superior perceptual skills outside of imaging, and as such there is no accepted or principled basis to choose radiology trainees that will be most likely to attain mastery. In addition, research has demonstrated that perceptual expertise peaks earlier than factual knowledge and begins very early in training (Ravesloot et al., 2017). Unfortunately, perceptual expertise also appears to plateau at a high level of error, accounting for the persistent high levels of error noted since Garland's pioneering work in the 1940s (Garland, 1949).

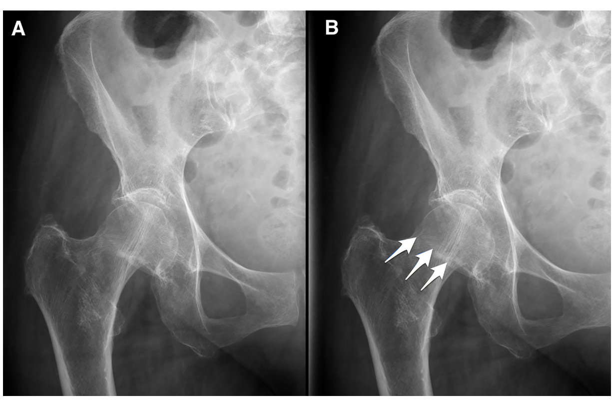

FIGURE 8 | Reprinted from Chen et al. (2017) with permission. **(A)** Example of an image shown during perceptual training of hip fracture identification. **(B)** Arrows represent the feedback provided in case of a wrong answer. Top novices achieved expert level accuracy in hip fracture detection in under 1 h of perceptual training (Chen et al., 2017).

Even with our current understanding of the nature of radiologic expertise, and how it develops during residency, significant gaps in knowledge remain. Importantly, these include translation of the knowledge base into concrete methods for radiologists to decrease interpretive error. Peak expertise is currently achieved by radiologists only after years of trial-and-error, resulting in the learning of hidden principles that have not yet been articulated, and as such are not explicitly recognized or consistently applied. Until we understand the precise perceptual criteria that radiologists apply to discriminate abnormalities in medical images, the field as a whole will not achieve peak performance.

The ability of a radiologist to see abnormalities largely depends on their skill to recognize subtle shapes and textures embedded in a noisy background. Radiologic expertise may therefore constitute the solution to a complex texture discrimination problem. If so, expert radiologists may learn to rapidly detect abnormalities in their peripheral vision, and then use this information to target central vision for deeper analysis. This idea differs from previous suggestions about the perception of textures in visual performance in radiology (Balas et al., 2009; Whitney and Yamanashi Leib, 2018) in that here we refer to texture in the most general possible sense. Although classical image statistics, such as contrast, entropy, and the correlation between central and nearby pixel intensities, are thought to guide ocular fixation targeting, these statistics are not necessarily task relevant and therefore do not provide a complete picture of the relationship between informativeness and ocular targeting (McCamy et al., 2014).

We hypothesize that it is the correlated combination of the cardinal dimensions—the basis of visual texture (Bergen and Adelson, 1988; Bergen, 1991)—that expert radiologists may use to detect abnormalities. That is, just as both woody and granite textures can share the same cardinal image statistics, they nevertheless appear dissimilar due to their different textures (they are visual metamers with respect to their first-order statistics, but not in their second-order statistics). Prior work on texture statistics in radiological diagnosis has focused on individual texture features (i.e., "co-occurrence"), or specific (non-general) types of potentially relevant textures to radiology, while ignoring or actively removing information from other aspects of texture (i.e., orientation) (Hu et al., 2016). Previous studies also suggest that adding specific textures to objects in films can increase their visibility (Vittitoe et al., 1997). However, these previous studies necessarily chose what they felt were relevant textures, and their choices were to some extent arbitrary (as there is no established principle to know which textures are critical). Here, we propose that the field of radiology should determine the relevant textures from the entire space of second-order statistics that the human visual system can perceive. This approach entails the employment of a general model of texture statistics (Heeger and Bergen, 1995; Portilla and Simoncelli, 2000; Freeman and Simoncelli, 2011) to ascertain empirically, from the entire space of possible textures, which features are diagnostically informative. Such a strategy is likely to result in a principled and non-arbitrary set of informative textures that represent the difference in perceptual abilities between experts and novices (Armato et al., 2011). Once known, specific perceptual learning heuristics could be designed to train for enhanced detection of those particular textures.

The proposed model would fit all known results to the best of our knowledge, and is supported by studies showing that experienced radiologists tend to have longer saccadic lengths between fixations, suggesting that they are better able to see targets further out in their peripheral vision (and use them to target subsequent fixations) than novices (Alzubaidi et al., 2010). Extensive training may enable radiologists to perceptually learn to detect abnormal textures at increased retinal eccentricities, earlier in their instruction and more consistently. It follows that analysis of fixation consistency across radiologists (a measure of image 'informativeness') may account for both bottom–up and top–down influences on image exploration (McCamy et al., 2014).

CONCLUSION

Despite recent improvements in computer aided detection (CAD) and machine learning algorithms, radiologic interpretation is likely to remain a human task for the foreseeable future. Although many radiologists are concerned about artificial intelligence (AI) displacing them, most scholars are now of the opinion that AI will *augment* rather than replace radiologists (Liew, 2018). In a future where radiologists are mandatory as component human authorities (Liew, 2018), educational and practical interventions to improve human perceptual and decision-making skills continue to be needed to improve accuracy and reduce medical error (Waite et al., 2017b; Ekpo et al., 2018).

Radiology must move past the declarative knowledge paradigm to advance its training models and decrease its long-standing high error rate. In short, simply informing radiologists about potential errors does not improve their perception.

We propose that one way to improve radiologic instruction is, first, to determine precisely what makes abnormalities different from normal tissue—as in which textures are most informative—and then specifically train physicians to detect these textures with their peripheral vision, to enhance their ability to find abnormalities in medical images. This knowledge could afford focused perceptual learning, thereby supplementing conceptual knowledge and providing the exposure to abnormalities required for sensitivity improvements to occur during residency, rather than waiting (and hoping) for them to develop during routine radiologic practice. Our review of the literature moreover indicates the need for a deeper understanding of expertise-related individual differences in oculomotor-behavior, especially with regard to the informativeness of image regions. By precisely characterizing the contributions from each of these skills to the radiologist's toolkit (and any potential overlap), we may be able to optimize heuristics for training on each of them.

As a field dominated by a primarily *perceptual* task, radiology needs a more refined understanding of perceptual expertise to improve accuracy, reduce error, and improve patient care.

AUTHOR CONTRIBUTIONS

SW conceived and wrote the manuscript. AG wrote an initial section of the manuscript and contributed to the figures and permissions. RA wrote a section of the manuscript. SM contributed to the editing of the manuscript. SM, MC, DH, and SM-C contributed to the conception of the work. SM-C was responsible for extensive editing. All authors contributed to the revising, reading, and approving the final version of the manuscript for submission.

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BRIEF RESEARCH REPORT
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Binocular Summation and Suppression of Contrast Sensitivity in Strabismus, Fusion and Amblyopia

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Purpose: Amblyopia and strabismus affect 2%–5% of the population and cause a broad range of visual deficits. The response to treatment is generally assessed using visual acuity, which is an insensitive measure of visual function and may, therefore, underestimate binocular vision gains in these patients. On the other hand, the contrast sensitivity function (CSF) generally takes longer to assess than visual acuity, but it is better correlated with improvement in a range of visual tasks and, notably, with improvements in binocular vision. The present study aims to assess monocular and binocular CSFs in amblyopia and strabismus patients.

Methods: Both monocular CSFs and the binocular CSF were assessed for subjects with amblyopia (n = 11), strabismus without amblyopia (n = 20), and normally sighted controls (n = 24) using a tablet-based implementation of the quick CSF, which can assess a full CSF in <3 min. Binocular summation was evaluated against a baseline model of simple probability summation.

Results: The CSF of amblyopic eyes was impaired at mid-to-high spatial frequencies compared to fellow eyes, strabismic eyes without amblyopia, and control eyes. Binocular contrast summation exceeded probability summation in controls, but not in subjects with amblyopia (with or without strabismus) or strabismus without amblyopia who were able to fuse at the test distance. Binocular summation was less than probability summation in strabismic subjects who were unable to fuse.

Conclusions: We conclude that monocular and binocular contrast sensitivity deficits define important characteristics of amblyopia and strabismus that are not captured by visual acuity alone and can be measured efficiently using the quick CSF.

Keywords: amblyopia and strabismus, contrast sensitivity function (CSF), quick CSF, visual acuity, binocular summation

INTRODUCTION

Amblyopia and strabismus are the most common developmental disorders of binocular vision, with an estimated prevalence of around 2%–5% (Graham, 1974; Ross et al., 1977; Friedmann et al., 1980; Cohen, 1981; Simpson et al., 1984; Stayte et al., 1990; Thompson et al., 1991; Satterfield et al., 1993; Kvarnström et al., 2001; Jakobsson et al., 2002; Barry and König, 2003; Robaei et al., 2005). Amblyopia affects the spatial vision of one or both eyes in the absence of an obvious organic cause and is associated with a history of abnormal visual experience during development (The Lasker/IRRF Initiative for Innovation in Vision Science, 2018). Strabismus impairs the ability to align the eyes so that targets are imaged on the fovea of the *fixing* eye and on parafoveal retina in the strabismic eye. The magnitude of strabismus may vary with viewing distance, such that some people with strabismus are able to fuse at some viewing distances (Hatt et al., 2008), and the strabismic deviation may be constant or intermittent (for review, see Helveston, 2010). Strabismus is associated with social difficulties (Satterfield et al., 1993; Olitsky et al., 1999; Jackson et al., 2006), a reduced quality of life (Tandon et al., 2014), elevated risk of sustaining musculoskeletal injury, fracture, or fall (Pineles et al., 2015b), and a negative impact on employment opportunities (Goff et al., 2006; Mojon-Azzi and Mojon, 2007).

Strabismus is a common cause of amblyopia (Woodruff et al., 1994b; Simons, 2005), although amblyopia can also be caused by other developmental disorders such as anisometropia or visual deprivation (Helveston, 2010). Amblyopia is associated with deficits in spatial vision (Robaei et al., 2005; Zhao et al., 2017) including reduced visual acuity (Kirschen and Flom, 1978; Levi and Klein, 1982, 1985; Kelly and Buckingham, 1998), contrast sensitivity loss (Hess and Howell, 1977; Levi and Harwerth, 1978; Bradley and Freeman, 1981; Kiorpes et al., 1999; McKee et al., 2003), spatial distortion (Pugh, 1958; Hess et al., 1978; Fronius and Sireteanu, 1989; Hess, 2001), abnormal contour integration (Hess et al., 1997; Hess and Demanins, 1998), and binocular acuity summation (Sireteanu, 1982; Chang et al., 2017) deficits.

The current standard treatment for amblyopia is to provide a period of refractive correction (Cotter et al., 2012), then to use occlusion (eye patching) or penalization (blurring eye drops) therapies that temporarily impair vision in the fellow eye and force the use of the amblyopic eye (for review, see Clarke, 2010). Strabismus may be treated surgically (Mets et al., 2004), with prism correction (Gunton and Brown, 2012), or with vision therapy (Scheiman et al., 2011; for review, see Rutstein et al., 2012). However, these treatments for amblyopia (Woodruff et al., 1994a; Pediatric Eye Disease Investigator Group, 2003; Fresina and Campos, 2014) and strabismus (Fresina and Campos, 2014) rarely restore normal binocular vision. Consequently, after treatment, many patients experience persistent interocular suppression (Holopigian et al., 1988; Hess, 1991; Harrad, 1996; Kwon et al., 2015) or deficits in stereoacuity (Stewart et al., 2013; Levi et al., 2015) and binocular acuity summation (Blake and Fox, 1973; Chang et al., 2017).

Visual acuity is the main clinical measure for functional outcomes. However, many studies have shown that contrast sensitivity remains impaired in the affected eye even after normal acuity has been achieved by amblyopia treatment (Regan et al., 1977; Sjöstrand, 1981; Rogers et al., 1987; Cascairo et al., 1997; Huang et al., 2007). In many cases, visual acuity deficits may be more evident with low- than high-contrast visual acuity tests (Pineles et al., 2013, 2014b, 2015a). Furthermore, the contrast sensitivity loss in amblyopia is spatial-frequency dependent, a property that cannot be assessed by high- or low-contrast visual acuity alone. In several studies the amblyopic eye showed reduced contrast sensitivity that mostly occurred at mid-high spatial frequencies, while deficits at low spatial frequencies were less common (Hess and Howell, 1977; Levi and Harwerth, 1977; Rentschler et al., 1980; Sjöstrand, 1981; Howell et al., 1983), suggesting a significant need for assessing spatial-frequency dependent deficits in characterizing amblyopic vision.

Although the contrast sensitivity function (CSF) of the fellow fixing eye remains normal or near normal in amblyopia (Cascairo et al., 1997), binocular summation is greatly compromised or absent in amblyopia (Levi et al., 1980; Sireteanu et al., 1981; Pardhan and Whitaker, 2000; Hess et al., 2014) unless the sensitivity deficit of the amblyopic eye is compensated (Pardhan and Gilchrist, 1992; Baker and Meese, 2007; Baker et al., 2007a). In principle, the binocular summation deficit could arise from impaired mechanisms of binocular interaction that are not spatially-selective (Huang et al., 2011). Alternatively, it may depend on structural correlations, which may show spatial frequency selective effects of inter-ocular refractive differences, as in anisometropia, Holopigian et al. (1986) or misaligned binocular receptive fields, as in strabismus (Thorn and Boynton, 1974). In subjects with intermittent strabismus, binocular summation may, therefore, depend on whether fusion is possible at the testing distance. These spatial-frequency dependent features of contrast sensitivity deficits make the CSF a good candidate for evaluating monocular and binocular vision in strabismus and amblyopia.

While the need for effective assessment of contrast deficits in the patient population has been recognized (Owsley and Sloane, 1987; Sebag et al., 2016) its clinical assessment has been frustrated due to the long testing times of psychophysical assessments (Mansouri et al., 2008). To examine the role of amblyopia and strabismus in binocular contrast summation, we therefore measured the full monocular and binocular CSFs with the quick CSF method (Lesmes et al., 2010; Dorr et al., 2013) in amblyopes, subjects with strabismus but not amblyopia (who were either able or not to fuse at near test distances), and normally-sighted controls.

METHODS

Participants

The study design included three groups: patients with: (1) strabismic, anisometropic, or mixed amblyopia (AMB);

(2) strabismus without amblyopia (SWA); and (3) normally sighted individuals (NSC). Inclusion and exclusion criteria were:

1. Clinical amblyopia is often defined as at least 0.2 logMAR interocular difference in acuity with best correction. Here, we adopted the clinical definition of amblyopia for our inclusion and exclusion criteria. Strabismic amblyopia was defined as a ≥0.2 logMAR interocular difference in best-corrected visual acuity (BCVA). Strabismus was defined as angular deviation between eyes of 5–50 prism diopters at either near or far viewing distances. Anisometropic amblyopia was defined as a 2-line or greater interocular difference (≥0.2 logMAR) in BCVA with tropia ≤4 prism diopters.
2. Strabismus without amblyopia was defined as ≤0.2 logMAR difference between the monocular BCVAs. Strabismus was defined as above. Intermittent strabismus with near fusion was defined as ≤4 prism diopters at 40 cm test distance.
3. Normal vision was defined as BCVA ≤0.0 logMAR or uncorrected VA ≤0.2 logMAR for both eyes without any latent or manifest ocular deviation other than phorias within normal limits.
4. Subjects with any known cognitive or neurological impairments were excluded.

Informed consent was obtained from subjects or (in addition to subjects' assent) from the parents or legal guardian of subjects aged <18 years, in accordance with procedures approved by the IRB of Boston Children's Hospital and complying with the Declaration of Helsinki. Enrolled patients underwent complete clinical examination, including best corrected visual acuity (ETDRS charts, letter-by-letter scoring was used), cycloplegic refractive error, stereopsis (Titmus Fly SO-001), ocular motility, binocular fusion (a Worth 4 dot test) and cover test at near and distance fixation. The angle of any heterotropia or heterophoria was measured by prism-and-cover test at near and distance fixation. We only report the measurements made at near fixation, which is relevant to the 60 cm viewing distance of CSF assessment. Minimum participant age was 5 years and all participants were able to perform letter acuity assessment. Participant characteristics are provided in **Table 1**. All subjects were tested with best-corrected vision in the CSF test; as can be seen in **Table 1**, there was some overlap of visual acuities between the groups (i.e., one out of 11 amblyopic eyes had better acuity than three normal eyes but with interocular difference ≥0.2 logMAR). For consistency across groups, hereafter we term the amblyopic eye and fellow eye as *the non-dominant eye (NDE)* and *dominant eye (DE)*, respectively. The DE was determined by the results from clinical binocular function or acuity test (for AMB and SWA subjects) or finger pointing task (for NSC).

Procedure

Spatial CSFs were assessed with the quick CSF method (Lesmes et al., 2010) and a 10-AFC letter recognition task (Hou et al., 2015) implemented on a tablet computer (Dorr et al., 2013). The quick CSF method is a Bayesian adaptive procedure that takes advantage of prior knowledge about the general shape of the CSF and searches the 2D stimulus space (contrast and spatial frequency) to find stimuli for future trials that maximize information about the subject's individual CSF.

The CSF maps a spatial frequency f to a sensitivity S by a truncated log-parabola $S(f, \theta)$ that is based on a log-parabola $S_0(f,\theta)$. The parameter vector Θ has four dimensions: (i) peak gain, $\gamma_{\max}$; (ii) peak spatial frequency, $f_{\max}$; (iii) bandwidth, β; and (iv) low-frequency truncation level, δ.

$$\log_{10}[S_0(f,\theta)] = \log_{10}(\gamma_{\max}) - \frac{4}{\log_{10}2}\left(\frac{\log_{10}(f) - \log_{10}(f_{\max})}{\beta}\right)^2$$

$$\log_{10}[S(f,\theta)] = \begin{cases} \log_{10}(\gamma_{\max}) - \delta & \text{if } f < f_{\max} \wedge \log_{10}S_0 < \log_{10}(\gamma_{\max}) - \delta \\ \log_{10}S_0(f,\theta) & \text{otherwise} \end{cases}$$

The quick CSF also provides two important scalar features: (i) a summary statistic, the area under the log CSF (AULCSF; Applegate et al., 1998) (ii) and the high spatial-frequency cut-off (CSF Acuity). Test letters were band-pass filtered Sloan letters with peak frequency of 0.64–41 cycles per degree (cpd) at the viewing distance of 60 cm. Each of 25 trials began with a 500 ms white bounding box cueing the size and location of the upcoming stimulus. Then, the target letter was presented for 2 s followed by a response interval. The experimenter entered the subject's response using a keyboard, which initiated a subsequent trial. No feedback was provided.

In random order, the CSF was measured binocularly and monocularly with each eye while the non-tested eye was occluded with an eye patch.

Data Analysis

During data recording, the quick CSF was initialized with a uniform prior. After data collection, all data sets were rescored with a more informative population prior (Dorr et al., 2017). As a summary statistic of binocular summation, we calculated the ratio of contrast sensitivity of the binocular to that of the dominant eye ($AULCSF_{Binocular}/AULCSF_{DE}$). For a finer-level analysis, we used the probability summation model, which is the simplest and most commonly used account in vision and hearing science (Dubois et al., 2013), as a theoretical yardstick. First, observers' thresholds for the NDE, DE, and binocular viewing conditions were each converted into the probability of detecting a target signal given the assumed psychometric function (Pelli, 1987; Klein, 2001; Dubois et al., 2013; Equation 1). This function $P(c, \tau)$ describes the probability of a correct response as a function of signal contrast c and threshold contrast τ:

$$P(c,\tau) = \gamma + (1 - \gamma - \lambda) \times \phi\left(\frac{0.6}{\beta} \times (c - \tau)\right) \quad (1)$$

where γ is guessing rate (= 0.1 for this 10-AFC paradigm), λ is the lapse rate, β is the slope of P (here, β = 0.25), and ϕ is the cumulative distribution function of the normal distribution. This conversion was made as a function of spatial frequency and the final probability for each viewing condition (non-dominant eye P_{NDE}, dominant eye P_{DE}, and binocular viewing

TABLE 1 | Participant characteristics.

			Amblyopia (*N* = 11)	Strabismus (*N* = 20)	Normal (*N* = 24)
Age (years)	mean (±SD)		15.9 (±16.2)	19.9 (±20.4)	18.7 (±10.8)
	min:median:max		6:9:50	5:9.5:68	5:17:43
Gender	ratio (female:male)		5:6	13:7	11:13
Visual Acuity (logMAR)	mean (±SD)	non-dominant eye	0.55 (±0.35)	0.09 (±0.11)	0.01 (±0.08)
		dominant eye	0.02 (±0.09)	0.05 (±0.09)	−0.04 (±0.08)
	min:median: max	non-dominant eye	0.14:0.48:1.30	−0.08:0.12:0.30	−0.12:0:0.18
		dominant eye	−0.12:0:0.18	−0.10:0.02:0.20	−0.22/−0.02/0.10
Angular Deviation (prism diopter)	mean (±SD)		10.2 (±14.8)	17.3 (±14.0)	Neither manifest nor latent deviation
	min:median:max		0:4:45	4:10:50	
Ability to fuse			*N* = 5	*N* = 7	*N* = 24
Strabismus type (intermittent)			NA	esotropia 7 (0) exotropia 6 (4) esophoria 4 (2) exophoria 3 (0)	NA

$P_{\text{Binocular}}$) was the mean probability across spatial frequencies. Next, we computed the expected probability summation derived from the probabilistic summation of monocular signals from the non-dominant and dominant eyes as shown in Equation 2.

$$P_{\text{Expected Binocular}} = P_{\text{NDE}} + P_{\text{DE}} - (P_{\text{NDE}} * P_{\text{DE}}) \qquad (2)$$

where P is the probability of detecting a target signal (corrected for the guessing rate of 10% by subtracting 0.1 from each term on the right-hand side and dividing by 0.9; for the left-hand side, this correction was inverted). We then compared this expected probability summation value $P_{\text{Expected Binocular}}$ to the probability of binocular viewing condition $P_{\text{Binocular}}$.

The posterior of the quick CSF provides a probability distribution over possible CSFs and their agreement with the data. We used the width of the credible interval, which encompasses 68.3% of the data, as a proxy to test-retest variability (Hou et al., 2016).

For statistical tests, we used a significance level of 0.05. Because a p-value tells us only how probable the observed outcome would be under the null hypothesis, but nothing about the relative probabilities for the null and H_1, we also report the false positive risk (FPR) for an assumed uniform prior (Colquhoun, 2014). For example, consider the comparison of summary statistic AULCSF between non-dominant eyes of the AMB subgroup (observed distribution of mean = 0.99, SD = 0.467) and NSC eyes (mean = 1.65, SD = 0.147). We then sampled 100,000 population samples (n = 11, the number of amblyopes) from normal distributions D_{AMB} and D_{NSC} with these parameters, and calculated how often the originally observed p-value of approximately 0.0009 would occur when comparing the observed distribution of NSC eyes against data under the null hypothesis (M_{NSC} = 3 times; note that this is different from the p-value *100,000 = ∼90 simulations where the effect size was at least as big as the originally observed effect) or a hypothesized true effect (M_{AMB} = ∼1,000). The ratio $M_{\text{NSC}}/(M_{\text{NSC}}+M_{\text{AMB}})$, which is influenced by statistical power of the experiment and the observed effect size and p-value, then gives us the FPR that we would see if the observed outcome was due to the null hypothesis being true; here, FPR = 0.003.

RESULTS

Data are publicly available at https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/3XWZUN.

Method Validation

The mean time to complete each quick CSF test was 170 (± 34) s, see **Supplementary Figure S1**. There was no effect of age on the reliability of quick CSF measurements, see **Supplementary Figure S2**.

Monocular Contrast Sensitivity Deficit in Amblyopia

We first analyzed the four parameter values of the quick CSF and its two summary estimates, AULCSF and CSF Acuity for the three groups.

The contrast sensitivity deficits of AMB patients can be seen in **Figure 1**, which shows average CSFs over the different groups, as well as boxplots of the CSF parameter distributions: the CSF for the non-dominant eye (red curve) is diagonally shifted downward and to the left of the dominant eye (blue curve).

More specifically, the AMB group showed a significant reduction in peak SF (from 3.89 to 1.94 cyc/deg; p = 0.001, Wilcoxon test; FPR = 0.002) and peak gain (from 1.89 to 1.77 log10 sensitivity; p = 0.032; FPR = 0.146) for the non-dominant eye. However, no significant difference was observed in bandwidth and in low SF truncation (p = 0.32 and p = 0.64, respectively), and SWA and NSC did not show a significant difference between the two eyes for any of the parameters.

The changes in peak SF and peak gain for the AMB group resulted in a pronounced AULCSF deficit in the non-dominant (but not dominant) eye relative to the NSC group (mean 1.68 and 0.99 vs. 1.65 log10 units; p = 0.608 and $p \ll 0.001$ (FPR = 0.003), respectively; two-sided t-test). AULCSF and

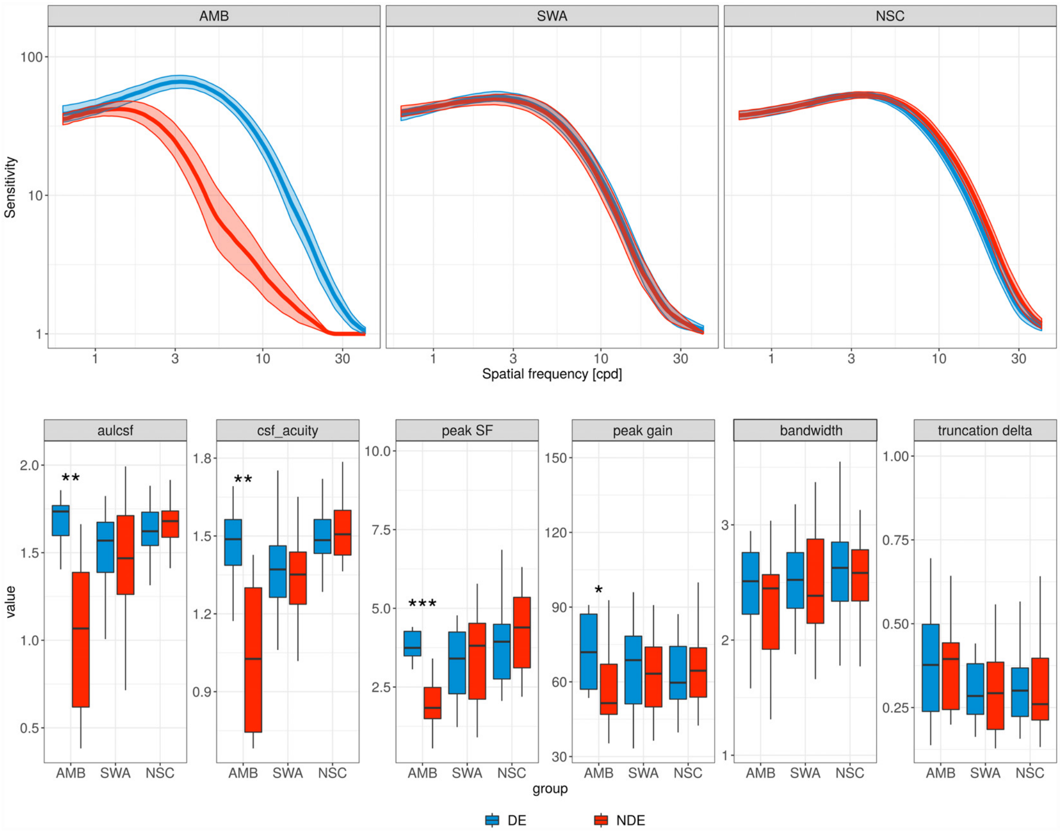

FIGURE 1 | Contrast sensitivity functions (CSFs). Top row, each panel contains the mean CSF of the non-dominant eye (red curve) and the dominant eye (blue curve) for the different subject groups. AMB, amblyopia; SWA, strabismus without amblyopia; NSC, normally sighted controls. Shaded areas represent ±1 standard error of the mean (SEM). Bottom row, parameter distributions of the observed CSFs. Boxplot midlines indicate median values; "*", "**," and "***" denote statistical significance (two-sided Wilcoxon test) at the alpha level of 0.05, 0.01 and 0.001, respectively.

CSF Acuity were also significantly lower in the non-dominant relative to the dominant eye ($p < 0.01$; FPR = 0.011 and 0.032, respectively) of AMB.

Binocular Contrast Summation

Figure 2 shows binocular summation index distributions. While NSC subjects show evidence of binocular contrast summation ($p \ll 0.001$, t-test; FPR $\ll 0.001$), there was no such evidence for AMB ($p = 0.14$) or SWA ($p = 0.09$), when all subjects were included in the analysis (blue boxes).

In principle, a lack of binocular summation may be due to disparate retinal correspondence that resulted from ocular misalignment of the strabismic vision rather than an absence of neural summation (Thorn and Boynton, 1974). Thus, we looked at those patients who were able to fuse their eyes at the testing distance. As shown by the red boxes in **Figure 2**, there remained a lack of binocular contrast summation for this AMB subgroup ($p = 0.17$). The summation index was significantly greater than 1 in SWA subjects who were able to fuse ($p < 0.003$, t-test; FPR = 0.013). These results suggest that in strabismus, the lack of binocular summation is a direct consequence of ocular misalignment, whereas in amblyopia there is an additional fundamental developmental deficit in binocular vision.

Understanding the Mechanism of Binocular Combination

It has been shown that the degree of binocular summation is greatly diminished with increasing interocular sensitivity difference (Marmor and Gawande, 1988; Pardhan and Gilchrist, 1990; Cagenello et al., 1993; Pardhan, 1993; Pineles et al., 2011) and depends on spatial frequency (Pardhan, 1996). We, therefore, compared the level of binocular contrast summation observed with the prediction of a probability summation model for independent sensory inputs.

We converted contrast sensitivity for the binocular condition of each observer to contrast detection threshold (probability correct 0.53) at 1,000 spatial frequencies (0.64∼41 cpd). Based on (Equation 1), we computed the probability of a correct response at that contrast in the monocular conditions. These probabilities were averaged across spatial frequencies. Lastly, we computed the expected binocular detection probability based on the probability summation of the monocular detection probabilities (Equation 2).

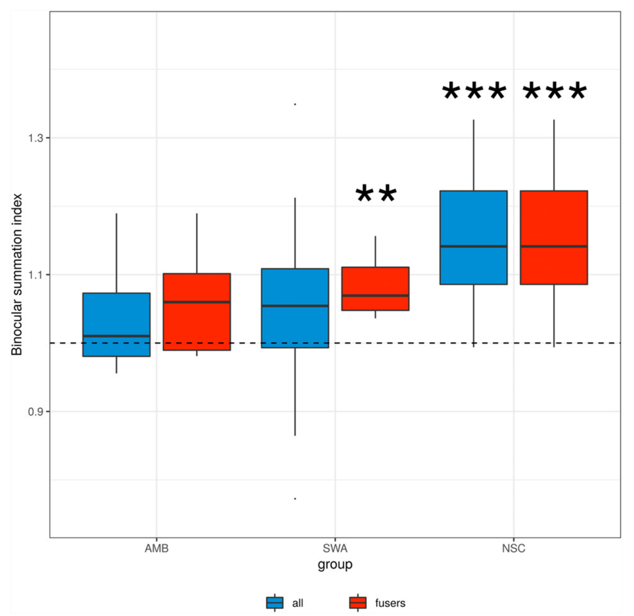

FIGURE 2 | Binocular summation index. Binocular summation was evaluated as the ratio of contrast sensitivity of binocular vision to that of the dominant eye ($AULCSF_{Binocular}/AULCSF_{DE}$). Blue boxes indicate the data from all subjects in each group, red boxes indicate the data from the subset of amblyopic and strabismic subjects who are able to fuse at the testing distance. "**" and "***" denote statistical significance (two-sided *t*-test) at the alpha level of 0.01 and 0.001, respectively. SWA subjects who were able to fuse and NSC subjects showed an index significantly greater than 1, i.e., binocular summation.

Data points in **Figure 3** show the probability of target detection in each viewing condition. Dotted lines indicate the observed binocular target detection probability (0.53). As expected, AMB exhibited considerable difference in target detection probability between both eyes ($p < 0.01$, Wilcoxon test; FPR = 0.079) while SWA and control groups did not show any significant differences between the two eyes (all $p > 0.05$).

For AMB subjects (with and without the ability to fuse the monocular images) and those SWA subjects that were able to fuse (**Figure 3** top left and bottom row, left and center), the observed binocular contrast summation did not differ from that predicted from simple probability summation (all $p > 0.05$, *t*-test). Binocular summation of NSC subjects, however, was significantly greater than predicted from the probability summation ($p < 0.008$; FPR = 0.020). For the subset of SWA subjects who were unable to fuse (**Figure 3A** center), this pattern reversed and binocular summation was significantly impaired relative to probability summation ($p < 0.02$; FPR = 0.088).

Relationship Between Visual Acuity and CSF Parameters

There were significant correlations between logMAR acuity and quick CSF measures both for the non-dominant eye and for interocular differences with r^2 values between 0.54 and 0.65 (all $p \ll 0.001$). Variability of logMAR acuity can be well-accounted for by log CSF Acuity ($r^2 = 0.64$). Slightly less accountability ($r^2 = 0.55$) was observed in the regression of logMAR acuity on AULCSF (see **Supplementary Figure S3**).

DISCUSSION AND CONCLUSION

Amblyopia is associated with anomalies in contrast sensitivity (Howell et al., 1983; McKee et al., 2003). Consistent with earlier findings, the present study demonstrates that individuals with amblyopia show a significant loss of contrast sensitivity in the non-dominant eye while the CSF of the dominant eye appears to be normal. By examining the CSF parameters, we show that the overall reduction in the CSF of the amblyopic eye was largely explained by significantly reduced peak spatial frequency and gain in the non-dominant eye. Because bandwidths stayed the same, sensitivity was lost particularly at high spatial frequencies. When we examined the monocular CSFs of SWA patients, we found no such differences in their monocular CSFs.

We also measured the deficits in binocular contrast sensitivity in AMB and SWA subjects. The superiority of binocular over monocular viewing is well documented in normal vision (Campbell and Green, 1965; Blake and Fox, 1973; Thorn and Boynton, 1974; Legge, 1984a). Binocular summation is often quantified as the ratio of binocular sensitivity to monocular sensitivity. While log probability summation for two equally detectable signals is approximately a factor of 1.2 (Tyler and Chen, 2000), many studies have shown that binocular contrast sensitivity is approximately 40% greater than monocular sensitivity (Legge, 1984b; Anderson and Movshon, 1989; Tyler and Chen, 2000; Meese et al., 2006; Baker et al., 2007b). Our NSC results are in good agreement with these estimates of binocular summation. Because this binocular performance enhancement exceeds the expected improvement from probability summation alone, it has been believed that this enhancement likely reflects neural summation (Campbell and Green, 1965; Blake and Fox, 1973; Bacon, 1976; Legge, 1984b; Anderson and Movshon, 1989).

Binocular contrast summation diminishes as interocular sensitivity difference increases (Marmor and Gawande, 1988; Pardhan and Gilchrist, 1992; Jiménez et al., 2004; Pineles et al., 2013, 2015a). Thus, without compensating for the difference in sensitivity between the two eyes, binocular contrast summation in amblyopia is either absent or greatly compromised (Levi et al., 1979, 1980; Pardhan and Gilchrist, 1992; Baker and Meese, 2007). Consistent with previous findings for binocular acuity summation (Jiménez et al., 2004), our results confirmed the lack of binocular contrast summation (Lema and Blake, 1977; Levi et al., 1980; Sireteanu et al., 1981; Hess et al., 2014) in AMB subjects. We further show that binocular contrast summation is impaired in those SWA subjects who were unable to fuse at near distances; SWA subjects who were able to fuse, on the other hand, did exhibit significant binocular summation. These findings are in good agreement with studies showing that binocular acuity summation is greater in subjects with greater control over intermittent exotropia (Yulek et al., 2017) and that strabismus surgery to align the eyes can lead to improvements in

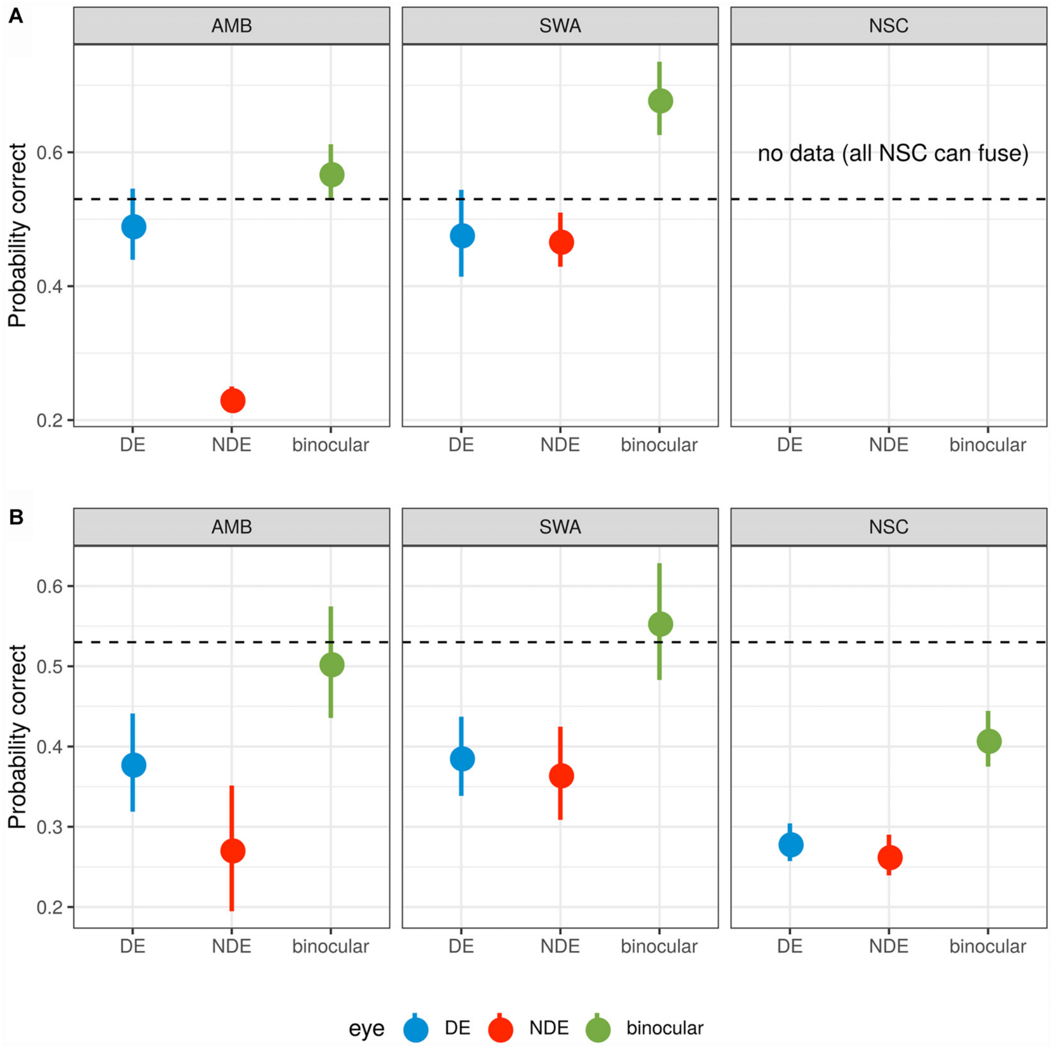

FIGURE 3 | Probability summation. **(A)** Subjects who were unable to fuse the two monocular images. **(B)** Subjects who were able to fuse. The dotted line indicates 53% threshold for binocular target identification. For the average contrast needed to reach this binocular threshold, monocular detection probabilities are shown for the non-dominant (red) and the dominant (blue) eye. Based on probabilistic summation of each eye's target detection probability, the expected probability for the binocular condition is shown in green. A value below the dotted line indicates that actual binocular summation exceeds probabilistic summation. A value above the dotted line indicates that the monocular images inhibit one another so that performance is worse than expected from target detection by independent monocular mechanisms. Error bars represent ±1 SEM.

binocular vision (Pineles et al., 2015a; Kattan et al., 2016; Chang et al., 2017).

We also used the monocular and binocular psychometric functions to estimate probability summation. The results confirmed the analyses of dominant eye and binocular AULCSF; the binocular contrast sensitivity of AMB or SWA subjects who were able to fuse was consistent with simple probability summation between independent detectors. This indicates an impairment of binocular contrast vision. Moreover, for SWA subjects who were unable to fuse at near distances, binocular contrast sensitivity was worse than expected from probability summation, suggesting an inhibitory process that impairs the combination of monocular sensitivity. These results are in good agreement with previous studies showing inhibition of binocular acuity summation in strabismic observers (Pineles et al., 2013, 2014a).

The use of the probability summation model allowed us to evaluate mechanisms of binocular interactions based on monocular and binocular CSFs when the two eyes have drastically different sensitivities. The method can be extended directly to many other visual conditions, such as age-related macular degeneration (AMD), glaucoma, and cataract. It can also be extended to other measures of visual function, such as monocular and binocular visual acuity, and monocular and binocular perimetry.

In conclusion, our results suggest that monocular and binocular contrast sensitivity deficits define important characteristics of amblyopia and strabismus that are not captured by visual acuity alone. Furthermore, our results identify a key role of fusion in binocular summation. Finally, measurement of both the monocular and binocular CSFs was possible rapidly and reliably even in young children, which may allow clinicians to more accurately assess individual patients' functional contrast sensitivity and acuity outcomes and prognosis.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with procedures approved by the IRB of Boston Children's Hospital with written informed consent from all subjects or (in addition to subjects' assent) from the parents or legal guardian of subjects aged <18 years. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the IRB of Boston Children's Hospital.

AUTHOR CONTRIBUTIONS

MYK, MK, KC, DH, Z-LL, and PB contributed to the conception and design of the study. AM collected the data and organized the database. MD, MYK, and LL analyzed the data. MD and PB wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2019.00234/full#supplementary-material

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frontiers in Human Neuroscience

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Evidence for the Rhythmic Perceptual Sampling of Auditory Scenes

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Converging results suggest that perception is controlled by rhythmic processes in the brain. In the auditory domain, neuroimaging studies show that the perception of sounds is shaped by rhythmic activity prior to the stimulus, and electrophysiological recordings have linked delta and theta band activity to the functioning of individual neurons. These results have promoted theories of rhythmic modes of listening and generally suggest that the perceptually relevant encoding of acoustic information is structured by rhythmic processes along auditory pathways. A prediction from this perspective—which so far has not been tested—is that such rhythmic processes also shape how acoustic information is combined over time to judge extended soundscapes. The present study was designed to directly test this prediction. Human participants judged the overall change in perceived frequency content in temporally extended (1.2–1.8 s) soundscapes, while the perceptual use of the available sensory evidence was quantified using psychophysical reverse correlation. Model-based analysis of individual participant's perceptual weights revealed a rich temporal structure, including linear trends, a U-shaped profile tied to the overall stimulus duration, and importantly, rhythmic components at the time scale of 1–2 Hz. The collective evidence found here across four versions of the experiment supports the notion that rhythmic processes operating on the delta time scale structure how perception samples temporally extended acoustic scenes.

Keywords: hearing, auditory perception, rhythmic perception, reverse correlation, perceptual weights, delta band, theta band

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INTRODUCTION

Perception seems to be systematically controlled by rhythmic processes in the brain (VanRullen, 2016; Haegens and Zion Golumbic, 2018; Helfrich, 2018). These rhythmic processes may for example reflect the excitability sensory neurons (Lakatos et al., 2005; Romei et al., 2008; Kayser et al., 2015), the selection of specific features for a behavioral response (Wyart et al., 2012; Wostmann et al., 2016), or the attentional modulation of perception (Busch et al., 2009; Busch and VanRullen, 2010). The perceptually-relevant rhythmic brain activity not only manifests in systematic relations between brain and behavior, such as better perceptual detection rates following a specific pattern of brain activity (Ng et al., 2012; Henry et al., 2014; Iemi and Busch, 2018), but can also reflect directly in behavioral data: for example, reaction times or perceptual accuracies in visual detection tasks are modulated at time scales of theta (~4 Hz) and alpha (~8 Hz) band activity (Fiebelkorn et al., 2011; VanRullen and Dubois, 2011; Landau and Fries, 2012; Song et al., 2014). In the case of hearing, neuroimaging studies have similarly shown that pre-stimulus delta (∼1 Hz) and theta activity (∼4 Hz) determine whether a sound is detected or influence how it is perceived (Ng et al., 2012; Henry et al., 2014, 2016; Strauss et al., 2015; ten Oever and Sack, 2015; Kayser et al., 2016). As in vision, the influence of rhythmic activity manifests also in behavioral data (Barnes and Jones, 2000; Hickok et al., 2015; Ho et al., 2017). In general, the apparent influence of rhythmic neural activity on behavior has been linked to rhythmic modes of perception, which facilitate the amplification of specific, e.g., expected, stimuli and mediate the alignment of endogenous neural activity to the regularities of structured sounds such as speech (Schroeder and Lakatos, 2009; Giraud and Poeppel, 2012). Indeed, the time scales of human perceptual sensitivity and the time scales at which rhythmic auditory activity shapes perception seem to be well matched (Edwards and Chang, 2013; Keitel et al., 2018).

While it remains unclear whether truly spontaneous brain activity affects auditory perception (VanRullen et al., 2014; Zoefel and VanRullen, 2017), it is clear that once the auditory system is driven by sounds rhythmic activity becomes engaged and shapes perception (Henry et al., 2014; Zoefel and VanRullen, 2015, 2017; Lakatos et al., 2016; Haegens and Zion Golumbic, 2018). Still, many studies linking neural activity and auditory percepts have relied on brief acoustic targets, such as tones (Ng et al., 2012; Kayser et al., 2016; McNair et al., 2019), gaps in noise (Henry and Obleser, 2012; Henry et al., 2014), or isolated words or syllables (Strauss et al., 2015; ten Oever and Sack, 2015). Yet, a key prediction from models postulating a rhythmic mode of perception (Schroeder and Lakatos, 2009; Zoefel and VanRullen, 2017; Haegens and Zion Golumbic, 2018), and from models linking cortical delta activity with sensory gain (Kayser et al., 2015; Iemi and Busch, 2018), is that this rhythmic activity should also shape how sensory information is integrated over time: the perceptual weighting of temporally dispersed acoustic information should be modulated at precisely those time scales at which neural activity has been shown to shape the detection or perception of brief and isolated sounds. Note that this precise hypothesis is distinct from the roles of rhythmic activity highlighted by work on the relevance of the pseudo-rhythmic structure of speech for comprehension (Rosen, 1992; Ghitza and Greenberg, 2009; Zoefel et al., 2015), by studies using rhythmic electric brain stimulation to enhance speech comprehension (Zoefel and Davis, 2017; Wilsch et al., 2018), or studies showing that various aspects of acoustic and linguistic information are represented in (pseudo-) rhythmic brain activity (Di Liberto et al., 2015; Daube et al., 2019; Yi et al., 2019).

We here tested this prediction directly at the level of behavior (Kayser, 2019). That is, we asked whether the perceptual use of acoustic information available in a continuous and extended (1 s or longer) stimulus is structured rhythmically at the delta/theta band time scale. To this end, we employed an acoustic variant of the frequently used visual random dot motion stimulus (Mulder et al., 2013). In our study, participants judged the overall direction of change in the perceived frequency content of soundscapes composed of a dense sequence of random tones, a specific fraction of which systematically in- or de-creased in pitch (**Figure 1A**). The level of sensory evidence available in each trial about the direction of frequency change was sampled independently in epochs of between 90 ms to 180 ms (in different versions of the task) allowing us to quantify the influence of the moment by moment varying acoustic evidence on participant's judgments (**Figure 1B**). Across four versions of this experiment, we found consistent evidence that the perceptual sampling of temporally extended sounds is structured by processes operating at the time scale of around 1–2 Hz.

MATERIALS AND METHODS

We report the data obtained from a total of 79 volunteers (age: 19–28 years, 67% female). The data was collected following written informed consent and briefing about the purpose of the study. Participants received either monetary compensation or course credits. All had self-reported normal hearing. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of Bielefeld University. The required sample size per experiment was set *a priori* to at least $n = 20$ based on recommendations for behavioral studies (Simmons et al., 2011). For two of the experiments, an number of 23 was collected as data collection proceeded partly in parallel. Seven participants that had participant in Experiment 1 also participated in Experiment 3. Additional data from 18 participants were collected but not analyzed, as the data did not comprise sufficiently many trials (see data exclusion below).

Acoustic Stimuli

Stimuli were presented *via* headphones (Sennheiser HD200 Pro) at an average intensity of 65 dB root mean square level (calibrated using a Model 2250 sound level meter; Bruel & Kjær, Denmark) while participants were seated in an acoustically shielded room. Stimulus presentation was controlled from Matlab (Mathworks) using routines from the Psychophysics toolbox (Brainard, 1997).

The acoustic stimuli ("soundscapes") consisted of 30 simultaneous sequences of pure tones (each tone had 30 ms duration, 6 ms on/off cosine ramps; zero inter-tone interval except the cosine ramp) that either increased or decreased in frequency and each sequence lasted four tones (see **Figure 1A** for a spectro-temporal representation). The initial frequency of each sequence was drawn independently (uniform between 128 Hz and 16,384 Hz), and each sequence in/decreased in steps of 20 cents. To construct a specific soundscape, each tone sequence started at a random position within the four-tone sequence, so that the start time of each sequence was independent of that of all others (hence all sequences had the same "life-time," but started at a random "age"). Also, the precise onset times of individual tones were jittered between sequences by (uniformly) up to 30 ms, to ensure that individual tones did not all present at the same time. Once a sequence reached the 4th tone, it was replaced by a new sequence starting at a random frequency. The impression of an overall in- or decrease in frequency over time was manipulated by changing the fraction of sequences that in- or de-creased. This fraction was coded as between 0 and 1, with 0.5 indicating half the sequences as in- and the other half as decreasing, and 1 indicating that all sequences increased. Each

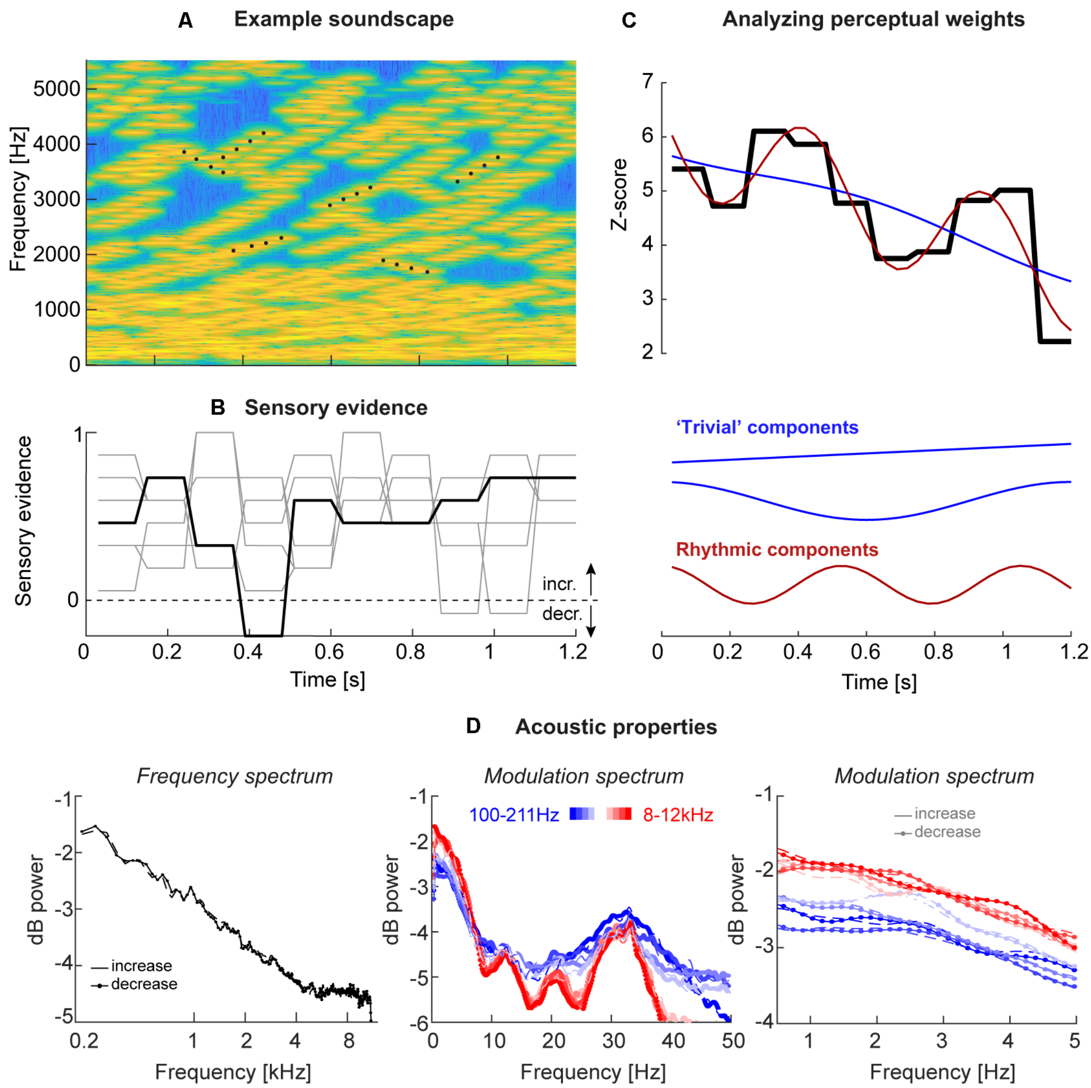

FIGURE 1 | Acoustic stimuli and analysis. **(A)** Stimuli consisted of "soundscapes" consisting of 30 four-tone sequences either in- or de-creasing in frequency (example sequences are marked by black dots). The fraction of sequences moving in the same direction changed randomly across trials and between "epochs" of a specific duration, which varied between experiments (see **Table 1**). **(B)** Each trial was characterized by the level of motion evidence for the soundscape to in- or de-crease, with the evidence being independent between epochs (periods of constant evidence) and trials, and varying around a participant-specific threshold. The black line presents the evidence for the soundscape shown in panel **(A)**, the gray lines the evidence for other trials, all with (on average) increasing frequency. An evidence of 1 correspond to a fully coherent soundscape, evidence of 0 to a completely random soundscape (15 tone sequences increasing, 15 decreasing). **(C)** The trial-averaged single participant perceptual weights (average sensory evidence for trials where participants responded with "up" or "down," combined after correcting the sign of down responses) were analyzed using regression models. These models distinguished trivial temporal structure arising from linear trends or U/V shaped profiles locked to stimulus duration (blue) from rhythmic structure at faster time scales (red). The black graph displays the perceptual weight of one example participant together with the best-fitting trivial and rhythmic contributions. **(D)** Acoustic properties of these soundscapes, shown here for Experiment 3. Upper panel: frequency spectrum revealing an approximate 1/f structure. Middle and lower panels: temporal modulation spectra, derived as the frequency spectrum of band-limited envelopes at different frequencies (color-coded). The middle panel reveals a peak at 33 Hz, the duration of individual tones. The right panel shows the lack of specific modulation peaks at the behaviorally relevant range between 1 Hz and 5 Hz, as well as a lack of difference between soundscapes with in- and de-creasing frequency content. All spectra are averaged across all trials and participants ($n = 20$; Experiment 3).

trial was characterized by the intended direction of change (in- or decrease) and the respective level of "motion evidence" at which this direction was expressed. Here motion evidence is defined as the deviation from ambiguous evidence (that is, 0.5). The relative motion evidence ranges from 0 (random) to 1 (fully coherent) and was used to characterize the task difficulty, and to quantify participant's perceptual thresholds (see **Figure 1B** for example traces).

To quantify the perceptual use of the acoustic information at different time points by individual participants, this motion evidence was manipulated 2-folds. First, for each participant, we determined (in an initial block) the participant specific perceptual threshold of motion evidence required to achieve around 80% correct performance (García-Pérez, 1998). To this end, participants performed the task based on trials with the task difficulty being determined following three interleaved 1-up 2-down staircases, each starting at a different level of difficulty (range 0.15–0.8), and using multiplicative reduction of step sizes. The threshold for each staircase was obtained from an average of six reversals, excluding the initial four reversals. The participant's threshold was then derived as the mean of the three individual thresholds.

Second, we manipulated the motion evidence between trials, and over time within a trial, around this subject-specific threshold. To this end, we sub-divided each soundscape into "epochs" and randomly and independently sampled the motion evidence from a Gaussian distribution around the participant-specific threshold (SD of 0.15 or 0.25, depending on the experiment). The duration of these epochs varied between experiments from 90 ms to 180 ms (see **Figure 1B** for examples; see **Table 1**). Practically, for a given trial, it was first determined whether the soundscape should in- or decrease. Then, the epoch-specific levels of motion evidence were drawn and then the sequences of individual tones were generated as described above. Thereby, the direction of sweep of each tone sequence could change at the start of a new epoch, where the directions of change of all sequences were re-drawn randomly to meet the momentary level of motion evidence. The total duration of each soundscape varied between 1,200 ms and 1,800 ms (**Table 1**). Each experiment consisted of 800 trials per participant. Inter-trials intervals lasted 800 ms to 1,200 ms (uniformly). For technical reasons, in some of the earlier Experiments (1 and 2) it had not been enforced that participants could respond only after the end of the soundscape, leading to premature responses. We hence imposed a minimal number of 750 valid trials for a participant to be included and we excluded data from 18 participants for Experiments 1 and 2 for this technical reason. Based on this criterion, we analyzed the data of $n = 23$ participants for Experiments 1 and 2, and $n = 20$ each for Experiments 3 and 4 (**Table 1**), whereby seven participants performed by Experiments 1 and 3.

Statistical Properties of the Acoustic Stimuli

Given the possibility that temporal structure of the acoustic envelope may shape the perceptual sampling of these soundscapes, we computed the temporal modulation spectrum in different frequency bands. To this end, we first computed the band-limited Hilbert envelope of each soundscape in 10 logarithmically spaced bands between 100 Hz and 12 kHz (3rd order Butterworth filter; Chandrasekaran and Ghazanfar, 2009). We then computed the average temporal modulation (frequency-) spectrum for each band across soundscapes and participants, separately for trials with in- or de-creasing frequency content (**Figure 1D**).

Response Templates

In the domain of motion evidence, each trial consists of a sequence of statistically independent samples of evidence for the direction of change in the soundscape. Hence, in this domain one can use the epoch by epoch evidence in a psychophysical reverse correlation procedure (Marmarelis, 1978; Eckstein and Ahumada, 2002). To compute perceptual weights (also known as response templates), trials were split according to direction of change and participants' responses. Then response-specific averages of the motion evidence were computed and were converted to units of z-scores within each participant using bootstrapping: the actual weights were standardized relative to the distribution of 4,000 sets of surrogate weights (Neri and Heeger, 2002; Chauvin et al., 2005). These weights indicate how strongly the acoustic evidence at each moment influences the perceptual judgments, with zero indicating no influence and positive values indicating that the in- (de)creases in the stimulus were rated as in- (de)creasing by the participant (see **Figure 2A**). To visualize the spectral composition of these templates we computed their power spectrum after standardizing the overall signal power (**Figure 2B**). It should be noted that this calculation makes the assumption that the perceptual weight, and any temporal structure therein, is consistent across trials within a participant, as the reverse correlation tries to assign a fixed (relatively high or low) weight to each epoch. Please note that due to the different duration of the epochs across experiments, the range of frequencies at which rhythmic patterns in behavioral can be recovered vary (2.75, 5.5, 4.15, and 4.15 Hz, respectively).

Analysis of Rhythmic Components in Response Templates

The main goal of the analysis was to determine whether the participant-specific weights were characterized by a significant rhythmic component (see **Figure 1C** for example weights). To this end an analysis was implemented that first selectively extracted non-rhythmic structure, such as: (i) the overall offset; (ii) a linear in- or de-crease over time; and (iii) a U/V shaped profile time-locked to the stimulus duration (modeled as $\cos(2^{*}pi^{*}t^{*}F_{exp})$, with F_{exp} = 1/stimulus duration). For each participant's perceptual template, we computed regression

TABLE 1 | Parameters and results for each experiment, including the duration of sound scape and the "epochs" over which the sensory evidence changed randomly, the number of epochs (sampling frequency) over which the perceptual weights were determined (Df), the number of participants (N), the best frequency determined by each model criterion (Fpeak) and the relative model criterion vs. the best trivial model.

	Soundscape	Epoch	*Df*	*N*	*F*peak cv-AICc	Δcv-AICc	*F*peak WAIC	ΔWAIC
Experiment 1	1,800 ms	180 ms (5.5 Hz)	10	23	1.6 Hz	183	1.6 Hz	186
Experiment 2	1,600 ms	90 ms (11 Hz)	17	23	1.3 Hz	32	1.3 Hz	71
Experiment 3	1,200 ms	120 ms (8.3 Hz)	10	20	2 Hz	121	2 Hz	135
Experiment 4	1,700 ms	120 ms (8.3 Hz)	14	20	1.2 Hz	13	2 Hz	46

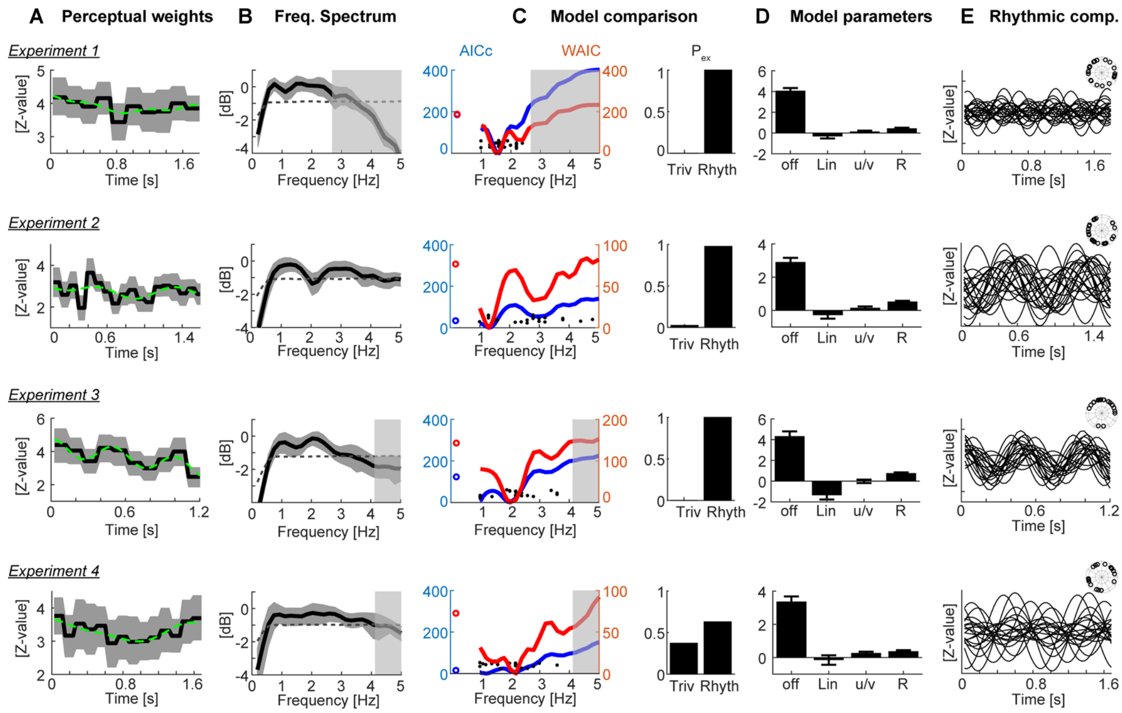

FIGURE 2 | Results. **(A)** Participant-averaged perceptual weights (black solid) with group-level two-sided 5% bootstrap confidence intervals (gray area) and the best-fitting model (green dashed). Units are in z-scores relative to a within-participant bootstrap baseline. **(B)** Participant-averaged frequency spectrum of the perceptual weights (black solid), with two-sided 5% bootstrap confidence interval (gray area). The dashed line represents the average spectrum obtained after time-shuffling the weights. **(C)** Model comparison results. The left curves show the group-level cv-AICc (blue; left y-axis) and watanabe-akaike information criterion (WAIC; red; right y-axis) values for the best trivial model (open circles) and frequency dependent models. Individual participant's best frequencies are denoted by solid black dots. The bars on the right show the exceedance probabilities of a comparison between the trivial model and the rhythmic model derived at the frequency yielding the lowest group-level cv-AICc. **(D)** Model parameters (betas) of the trivial contributions (offset, linear slope, u/v shaped profile) and the rhythmic component (R, root-mean-squared amplitude of sine and cosine components). Bars and error-bars indicate the group-level mean and SEM. **(E)** Rhythmic component of the best-fitting model for each participant (lines) and phase of this component each participant (inset). In panels **(B,C)** the gray transparent boxes black out those frequency ranges which cannot be faithfully reconstructed given the experiment specific epoch duration (i.e., behavioral sampling rate); hence only the clear regions are meaningful.

models comprising a collection of the non-rhythmic patterns (only i, i+ii, and i+ii+iii) and selected from these best fitting model based on the group-level AICc (see below). We then extended this "trivial" model by a rhythmic contribution modeled at frequencies varying between 1 Hz and 5 Hz, comprising both sine- and cosine components of the same frequency. The results were derived and are shown over a fixed frequency range, but the actually recoverable time scales differ between experiments, as the epoch duration, and hence the effective sampling rate of the perceptual weights differed. The interpretable range is indicated for each experiment in **Figure 2**.

Formal model-comparison was then used to determine, at the group-level, whether there was evidence for the rhythmic model to better explain the data than the trivial model (Burnham and Anderson, 2004; Gelman et al., 2014; Palminteri et al., 2017). That is, we tested whether the addition of a rhythmic component, e.g., at the delta band time scale, helped to explain more variance in the perceptual weights than models not featuring this rhythmic component. The comparison was based on the log-likelihoods computed for each participant's data and regression model. It is important to note that the inclusion of both sine and cosine components in the rhythmic model allowed for each participant to have a potentially different phase-alignment to the stimulus (see **Figure 2E** for the resulting best rhythmic components per participant).

Two recommended approaches for model comparison were used to compare the evidence in favor of each model, taking into account that the rhythmic model has additional degrees of freedom and may trivially explain the data better than the non-rhythmic model (Burnham and Anderson, 2004; Gelman et al., 2014; these additional degrees of freedom arise from the sine and cosine components). First, regression models were fit using a Monte-Carlo approach to compute the Watanabe-Akaike information criterion (WAIC), which captures the out-of-sample predictive power when penalizing each model (Gelman et al., 2014). This calculation was implemented using the Bayesian regression package for Matlab (Makalic and Schmidt, 2016), using 10,000 samples, 10,000 burn-in samples and a thinning factor of 5. Second, regression models were compared using a cross-validated version of the corrected Akaike criterion (cv-AICc; Hurvich and Tsai, 1991). Response templates were fit using half the data and the log-likelihood of each model was computed on the other half; the AICc was then averaged over 10 independent two-fold CV runs. Group-level comparison was performed by computing the group-level WAIC and cv-AICc, and by computing the exceedance probabilities of each model based on −0.5*cv-AICc [implemented using VBA toolbox in Matlab (Rigoux et al., 2014)].

To determine whether the selection of a specific frequency-dependent model over the trivial model was indeed specific to the behavioral data, and was not induced by any other factor in the analysis such as the temporal binning (see e.g., Vorberg and Schwarz, 1987) for pitfalls involved in testing reaction times for rhythmic patterns), we repeated the model comparison using randomized data (Zoefel et al., 2019). We randomly paired stimuli and responses and computed the probability of selecting the rhythmic model (at the group-level frequency determined using the original data) over the trivial model across 2000 instances of randomized data based on the cv-AICc.

The specific approach of contrasting the predictive power of different regression models, rather than e.g., testing the significance of specific regression parameters (here, of the sine and cosine terms of the rhythmic component), was chosen for a number of reasons. First, the use of cross-validation and Monte-Carlo methods allows capturing the out-of-sample predictive power of each model, while the obtained regression coefficients reflect only with specific-sample effect (Burnham and Anderson, 2004; Gelman et al., 2014). Second, a test on the regression parameters would need to consider the magnitude of the combined sine/cosine component, as the phase could differ between participants. This would require a somewhat problematic one-sided test on strictly positive values; and third, quantifying the predictive power of individual models allows a direct side by side comparison of the contribution of different rhythmic time scales to behavior, over and above the predictive power offered by a model without such a rhythmic component (that is, the respective AIC differences in **Figure 2C**).

RESULTS

Participants judged the perceived direction of frequency change in soundscapes constructed based on randomly varying task-relevant evidence. Across four variants of the experiment, the stimulus duration ranged from 1,200 to 1,800 ms, while the time scale at which perceptual weights were sampled varied between 5.5 Hz and 11 Hz (**Table 1**). These time scales were chosen *a priori* to allow capturing potential rhythmicity at time scales between 1 Hz and 10 Hz, as deemed relevant by a large body of neurophysiological and neuroimaging studies, and the combinations of soundscape and epoch duration were chosen to reflect of combinations of time scales. The frequency spectrum of these soundscapes followed largely a 1/f structure (**Figure 1D**) while the temporal modulation spectra of band-limited envelopes revealed no specific spectral peaks in the low-frequency range of interest, and no clear differences between directions of frequency change, that could have been exploited for behavior (1–5 Hz; **Figure 1D**).

Figure 2A displays the group-averaged perceptual weights for each experiment. The weights were significant for all time points (based on the 5% percentile of a bootstrap distribution). This is in line with the task difficulty being set to be around each participant's perceptual threshold and indicates that participants in large used the evidence from all time points to solve the task. For each dataset, the group-level weights exhibited a rich structure, comprising linear trends and a U/V shaped profile tied to the duration of each soundscape. To determine the contribution of such "trivial," i.e., non-rhythmic, contributions we fit three candidate models to each participant's data. Group-level model comparison revealed that the model featuring all three trivial factors (offset, slope, U/V profile) better explained the data than a reduced model: the group-level ΔAICc of the full vs. the reduced model were 211.2, 4.6, 93.3, 117.2 for Experiments 1–4, respectively, and the group-level exceedance probabilities of the full model were p_{ex} = 0.76, 0.49, 0.99, and 0.94. Only for Experiment 2 there was no clear evidence for any of the models to explain the data better than the others.

We then used the best trivial model (determined at the group-level, separately for each experiment) to quantify the extent to which the addition of a rhythmic contribution helped to better explain the perceptual weights. The prominence of temporal structure at the time scale between 1 Hz and 3 Hz is also highlighted by the frequency spectra in **Figure 2B**. Formal model comparison between the best trivial model and the frequency dependent models revealed that the addition of a rhythmic component between 1.2 Hz and 2 Hz significantly improved the model fit, even when taking into account the increased degrees of freedom (**Figure 2C**). The time scales best explaining the perceptual data were 1.6 Hz, 1.3 Hz, 2 Hz and 1.2 Hz based on the cv-AICc for the four experiments, respectively (**Table 1**). When using the WAIC, we found the same frequencies, except for Experiment 4 (here WAIC identified 2 Hz as best frequency). Both the cv-AICc and the WAIC model criteria identified the rhythmic model (defined at the group-level AICc-based best frequency) as significantly better than the trivial model for each dataset: the Δcv-AICc values of best rhythmic over the trivial model were 183, 32, 121, 13, respectively, the ΔWAIC values were 186, 71, 135, and 46 [with values >30 usually considered as very strong evidence in favor of one model (Burnham and Anderson, 2004)]. To further substantiate this result, we obtained group-level exceedance probabilities of the best rhythmic model in comparison to the trivial model: for three out of four experiments these clearly favored the rhythmic model: p_{ex} = 1, 0.97, 1, 0.62 for Experiments 1–4 (**Figure 2C**).

Given that this apparent rhythmic structure may also emerge simply as byproduct of sub-sampling the behavioral sensitivity at a fixed time scale, we repeated the model fitting after shuffling behavioral responses across trials (Zoefel et al., 2019). We computed the probability that the model incorporating the best group-level frequency derived from the original data better explained the data than the trivial model in the shuffled data (based on the cv-AICc): these probabilities were small and revealed the actual effects as (close-to) significant: p = 0.08, 0.076, 0.040, and 0.068 for Experiments 1–4, respectively.

To visualize the best models, **Figure 2D** displays the model parameters for the best-fitting rhythmic model, while **Figure 2E** displays the rhythmic component for each individual participant. In particular, for Experiment 3 the data reveal a clear alignment of perceptual weights across participants.

Closer inspection of **Figure 2C** shows that the WAIC reveals two local minima for several of the experiments: besides the overall best model at frequencies between 1.2 Hz and 2 Hz, also rhythmic components at frequencies between 2 Hz and 4 Hz better explain the actual data than the trivial model. The precise frequency of this second component varied between experiments (Experiment 1: 2.4 Hz, ΔWAIC = 123 vs. trivial model; Experiment 2: 2.8 Hz ΔWAIC = 43; Experiment 3: 3.4 Hz ΔWAIC = 36; Experiment 4: 3.8 Hz ΔWAIC = 24). This observation suggests that effectively multiple rhythmic components may underlie auditory perception.

DISCUSSION

We investigated whether the relation between the sensory evidence contained in temporally extended soundscapes and participant's judgments is governed by rhythmic components, as predicted by theories of rhythmic modes of listening, as well as studies linking delta/theta band neural activity with perception. The four experiments differed in the overall stimulus duration (**Table 1**; 1,200 ms to 1,800 ms) and the time scale at which perceptual weights were sampled (5.5–11 Hz). Despite these variations in the experimental paradigm, we found converging evidence that the perceptual sensitivity profiles contain relevant rhythmic structure at the time scales between 1.2 Hz and 2 Hz. That the rhythmic models indeed better explain the perceptual use of acoustic information than a trivial model only containing linear and U/V shaped trends is supported by the use of two criteria for formal model comparison and the comparison of the original and shuffled data. Importantly, the soundscapes used in the experiment did not exhibit obvious spectral structure at these behaviorally relevant times scales (see **Figure 1D**).

The perceptual weights featured pronounced non-rhythmic temporal structure, such as linear trends (e.g., Experiment 3, **Figure 2A**) or a U-shaped profile emphasizing early and late stimulus components (e.g., Experiment 4). Such stimulus-locked temporal sensitivity is frequently observed in perceptual decision-making paradigms and in part may reflect the participant-specific strategies for analyzing the sensory environment, temporal leakage in decision processes, or the urgency to respond (Okazawa et al., 2018; Waskom et al., 2018). Importantly, our results show that this sensitivity profile is augmented by a more rapidly changing temporal structure that emerges at precisely those time scales deemed relevant for auditory perceptual sensitivity by neuroimaging studies. Consistently across the four experiments, the best rhythmic models featured a perceptual sensitivity that was modulated with a frequency between 1.2 Hz and 2 Hz.

Previous work has shown that auditory cortical delta band activity is tied to changes in the network state related to an overall rhythmic fluctuation in neural background activity, visible both in spontaneous and acoustically driven states (Lakatos et al., 2005; Kayser et al., 2015; Guo et al., 2017). In particular strong engagement of auditory delta band activity has been implied in acoustic filtering of attended information and the task-relevant engagement of auditory networks (Lakatos et al., 2013, 2016; O'Connell et al., 2014) and plays a central role in theories of rhythmic modes of listening (Schroeder and Lakatos, 2009; Zoefel and VanRullen, 2017; Haegens and Zion Golumbic, 2018). While electrophysiological studies reporting behaviorally-relevant rhythmic patterns of brain activity often identified frequencies in the theta band as important (Henry and Obleser, 2012; Ng et al., 2012; Henry et al., 2014; Kayser et al., 2016) some of these have identified multiple mechanisms operating at different time scales, including the delta band between 1 Hz and 2 Hz (Henry et al., 2014, 2016; McNair et al., 2019). Our results corroborate the behavioral relevance of neural mechanisms operating in the delta band for auditory perception and provide evidence for the potential existence of distinct and possibly multiplexed rhythmic mechanisms. One potential interpretation of the results is that a specific listening mode is triggered by the onset of the soundscape and engages rhythmic processes that are phase-aligned across trials, but possibly engage distinct optimal phases across individuals (Henry et al., 2014; Haegens and Zion Golumbic, 2018). A related question, which only future studies can address, is whether the relative importance of rhythmic processes is stronger shortly following the onset of each soundscape, or is equally important throughout the entire soundscape.

An intriguing question is whether the precise time scale of sensory sampling is fixed, at least within a participant, or whether it adapts to the momentary statistics of the relevant sounds. Across the four experiments, we found a considerable variation in the best sampling frequency for each individual participant (see **Figure 2C**), and in the resulting group-level frequencies (1.6 Hz, 1.3 Hz, 2 Hz and 1.2 Hz, respectively, based on the cv-AICc), suggesting that these can vary across a considerable range. Is it possible that the sampling frequency is shaped by the experimental context, such as the duration of the soundscapes within each experiment? Only a systematic, and within-participant, manipulation of this duration can address this. In the present data, the ratio of sound duration to sampling time scales ranged from 2.04 to 2.8. This could be taken as evidence against a fixed alignment of sampling frequency to stimulus duration, and rather speaks in favor of more idiosyncratic mechanisms. A related question is whether the contribution of different time scales to rhythmic perceptual sampling is shaped by the overall spectral or temporal modulation statistics of the stimulus (see **Figure 1D**). Again, a systematic manipulation of such sound properties is required to address whether e.g., the reduced weight of higher sampling frequencies is related to the reduced temporal modulation energy at these frequencies. It seems unlikely, but cannot be fully excluded, that perceptual sampling actually operates at a fast time scale than the epoch-based manipulation of sensory evidence, and simply is seen between 1 Hz and 2 Hz as a result of aliasing (the perceptual weights were effectively sampled at frequencies between 2.75 Hz and 5.5 Hz, depending on the experiment). Hence, any behavioral sampling occurring in the alpha band (about 8–12 Hz), such as known from visual or auditory spatial attention, may effectively be seen at lower frequencies in the present data (Landau and Fries, 2012; VanRullen and Macdonald, 2012; Wostmann et al., 2016).

Still, there are a few caveats to note. First, while the converging evidence across the four experiments is convincing, for each individual experiment the statistical likelihood of the rhythmic model to better explain the data than the trivial model in comparison to randomized data was only marginally significant. One possibility is that the estimated perceptual weights are noisy and more trials per participant would be required to obtain fully reliable estimates. Second, it could be that the preferred perceptual sampling frequency differs across participants, precluding a reliable estimate of a common group-level model. Indeed, the single-participant data reveal a considerable variability in their best-frequency (see **Figure 2C**). However, without the assumption of a fixed group-level frequency, it becomes difficult to determine whether a frequency dependent model fits the data significantly better than a null model. Third, and along similar lines, the present analysis makes the assumption that the time course of these weights is consistent across trials. Such a consistency may not be warranted, but rather the trial-specific sampling may be aligned to trial-to-trial variable neural processes (Ng et al., 2012; Henry et al., 2014). Only the inclusion of neuroimaging in future studies can dissociate these possibilities. Fourth, the presented analysis implicitly assumes that the participants made use of the full available acoustic information and used all tone sequences equally for their judgments. The perceptual reverse correlation procedure was implemented in the domain of the overall motion-evidence, based on which the different tone sequences were randomly assembled. Performing a reverse correlation in the full time-frequency domain would likely require much higher trial numbers as the degrees of freedom for the perceptual weights would increase considerably. As a result, participant specific biases towards particularly low or high sound frequencies may have reduced the power of the present analysis. Considering the degrees of freedom of the analysis, that is the number of effective weights per perceptual template, **Table 1** reveals that the two experiments with the lowest number of free parameters were those yielding the larges evidence in favor of a rhythmic model, regardless of the total duration of the soundscape. This observation fits with the possibility that when sampling perceptual weights at finer temporal resolution or over additional dimensions, such as sound frequency, more trials would be required to obtain reliable estimates.

Also, the present results leave it unclear whether the rhythmic process(es) operate at the level of sensory encoding or decision making. When combined with fixed-duration stimuli, psychophysical reverse correlation cannot dissociate sensory from decision processes (Okazawa et al., 2018). While electrophysiological studies have directly demonstrated the relevance of auditory cortical delta band activity for neural sound encoding (O'Connell et al., 2014; Kayser et al., 2015) and perception (Lakatos et al., 2016), neuroimaging studies have shown that rhythmic brain activity may affect both the encoding of sensory information at shorter latencies and decision processes emerging later in frontal regions (Kayser et al., 2016; McNair et al., 2019). Work on visual decision making has also demonstrated the relevance of delta band activity for the accumulation of sensory evidence over time (Wyart et al., 2012). Hence it could be that the rhythmic patterns revealed here either reflect a change in the quality of the encoding of sensory evidence at each moment in time, which then results in a differential contribution to the participant's judgment, or a direct change in the weight assigned during the accumulation of evidence for choice (Wyart et al., 2012; Drugowitsch et al., 2016). More work is required to better understand the interplay of rhythmic processes related to sensory encoding and of those related to the actual decision process.

To conclude, theories of rhythmic modes of listening, and neurophysiological data linking network activity to single neuron encoding, predict that rhythmic activity shapes how acoustic information is combined over time to judge extended soundscapes. The present study proposes one approach to test this and provides converging evidence in support of this prediction. Future work can capitalize on this approach to directly link electrophysiological signatures of rhythmic activity to the perceptual combination of acoustic information over time.

DATA AVAILABILITY

The behavioral data and the required Matlab code for producing the stimuli, the analysis and figures are available from http://www.uni-bielefeld.de/biologie/cns/resources.html.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Bielefeld University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CK conceived and implemented the study, analyzed the data, wrote the manuscript.

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Altered Functional Connectivity in Patients With Sloping Sensorineural Hearing Loss

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Background: Sensory deprivation, such as hearing loss, has been demonstrated to change the intrinsic functional connectivity (FC) of the brain, as measured with resting-state functional magnetic resonance imaging (rs-fMRI). Patients with sloping sensorineural hearing loss (SNHL) are a unique population among the hearing impaired, as they have all been exposed to some auditory input throughout their lifespan and all use spoken language.

Materials and Methods: Twenty patients with SNHL and 21 control subjects participated in a rs-fMRI study. Whole-brain seed-driven FC maps were obtained, with audiological scores of patients, including hearing loss severity and speech performance, used as covariates.

Results: Most profound differences in FC were found between patients with prelingual (before language development, PRE) vs. postlingual onset (after language development, POST) of SNHL. An early onset was related to enhancement in long-range network connections, including the default-mode network, the dorsal-attention network and the fronto-parietal network, as well as in local sensory networks, the visual and the sensorimotor. A number of multisensory brain regions in frontal and parietal cortices, as well as the cerebellum, were also more internally connected. We interpret these effects as top-down mechanisms serving optimization of multisensory experience in SNHL with a prelingual onset. At the same time, POST patients showed enhanced FC between the salience network and multisensory parietal areas, as well as with the hippocampus, when they were compared to those with PRE hearing loss. Signal in several cortex regions subserving visual processing was also more intra-correlated in POST vs. PRE patients. This outcome might point to more attention resources directed to multisensory as well as memory experience. Finally, audiological scores correlated with FC in several sensory and high-order brain regions in all patients.

Conclusion: The results show that a sloping hearing loss is related to altered resting-state brain organization. Effects were shown in attention and cognitive control networks,

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as well as visual and sensorimotor regions. Specifically, we found that even in a partial hearing deficit (affecting only some of the hearing frequency ranges), the age at the onset affects the brain function differently, pointing to the role of sensitive periods in brain development.

Keywords: functional connectivity, resting state, sensorineural hearing loss, partial deafness, neuronal plasticity

INTRODUCTION

The brain develops the capability of a complex form based on its genetic makeup, that is modified by its sensory experience (Kral and Eggermont, 2007; Ballantyne et al., 2008). The structural and functional organization of the brain occurs throughout life as a result of repeated engagement within specific neural systems to process ongoing information (Guerra-Carrillo et al., 2014). For some functions, however, such as developing certain auditory, visual, and language abilities, there seems to exist sensitive developmental periods during which the nervous system is especially responsive to certain incoming stimuli (Daw, 2009; Friederici, 2012; Gordon et al., 2013; Kral, 2013). If stimulation is disrupted in these early life periods, for instance due to sensory deprivation, the neuronal organization might become irreversibly altered (Cardon et al., 2012; Kral and Sharma, 2012; Voss, 2013; Friedmann and Rusou, 2015; Gordon et al., 2015).

One MRI technique, which may serve as a window into experience-related brain development and plasticity, particularly, is resting state functional magnetic resonance imaging (rs-fMRI). It measures low-frequency spontaneous fluctuations of blood oxygen level-dependent (BOLD) signals across the whole brain. This effect was first described by Biswal et al. (1995), Zhang and Raichle (2010). Rs-fMRI benefits from the fact that the brain at rest retains its inherent functional organization (also termed, functional connectivity, FC) and thus temporal correlations between various brain regions are hypothesized to reflect prior coincidental neural firing.

Several canonical resting state networks (RSN) can be reproducibly identified using a variety of analysis approaches (Smitha et al., 2017). These include networks that are enhanced during the performance of specific tasks, such as the salience network (SN) for selection of useful information from the environment, the fronto-parietal (FPN) network involved in task monitoring, the dorsal (DAN) and ventral (VAN) attention networks, the language network, as well as several sensory networks (e.g., visual, auditory, sensorimotor). The only RS network that decreases its activity during attention-demanding tasks is the default mode network (DMN), underlying unconstrained, conscious cognition (Greicius, 2008).

Sensory deprivation resulting from blindness or deafness provides an excellent opportunity to study experience-dependent brain plasticity (Finney et al., 2001; Bock and Fine, 2014; Sharma et al., 2015). Similar to other conditions leading to adverse behavioral performance (Kelly et al., 2008), including aging and neurodegenerative diseases (Hohenfeld et al., 2018) as well as mental disorders (Azeez and Biswal, 2017), sensory deprivation has been widely demonstrated to change intrinsic FC (in auditory deficits: Burton et al., 2012; Maudoux et al., 2012; Schmidt et al., 2013; Husain et al., 2014; Li et al., 2015; Liu et al., 2015; Ding et al., 2016; Sabbah et al., 2016; Hofmeier et al., 2018; Luan et al., 2019a,b; Rosemann and Thiel, 2019; Xu et al., 2019c,b; in visual deficits: Burton et al., 2014).

Nevertheless, only scarce literature exists on brain resting brain network changes in patients with moderate to severe hearing loss, as is the case in the current study (Schmidt et al., 2013; Husain et al., 2014; Puschmann and Thiel, 2017; Xu et al., 2019c). The findings include increased functional couplings between frontal and parietal regions (Schmidt et al., 2013, Husain et al., 2014) and within the parietal cortex (Schmidt et al., 2013), decreased (Xu et al., 2019a) or increased (Schmidt et al., 2013) FC from insula to the inferior parietal cortex, decreased (Husain et al., 2014) or increased (Puschmann and Thiel, 2017) signal correlations between auditory and visual cortices, decreased FC between the insula and sensorimotor as well as high-order frontal brain areas (Xu et al., 2019c), and increased or decreased couplings between frontal and visual or sensorimotor sensory regions (Puschmann and Thiel, 2017 and Husain et al., 2014, respectively).

Although some convergence can be seen in the published findings, suggesting the involvement of additional cognitive resources as well as possible enhanced collaboration between sensory regions indicating compensatory plasticity in hearing loss, the outcomes of the existing studies are hardly comparable. Besides the fact that diverse patient populations have been studied (in terms of the accompanying tinnitus, age, etiology of HL) and they were mostly very limited in size, the above-mentioned experiments selected only specific networks for the analysis [e.g., only auditory, DMN and DAN in Schmidt et al. (2013) and in Husain et al. (2014); visual cortex in Puschmann et al. (2014)]. In addition, a variety of distinct methods and statistical thresholds were applied to quantify connectivity.

The purpose of the current study was to examine the effect of an auditory deficit in all RSNs. This seemed to be a particularly valid endeavor since deafness has become perceived as a “connectome disease,” i.e., affecting whole brain function, such as with cognitive and emotional processing, far beyond the auditory system (Cieśla et al., 2016; Kral et al., 2016). Specifically, we investigated a population with mid- to high-frequency sensorineural hearing loss (SNHL; also termed *partial deafness/PD,* Skarzynski et al., 2010). In addition, we explored whether measures of functional network organization between *various* brain areas are correlated with audiological performance in the patient group, including the severity of HL and speech understanding scores.

The population selected for this study was unique in that they represented patients with both prelingual hearing loss (congenital or developed early, before language acquisition) and postlingual hearing deficits which have, however, never been complete. All patients had been exposed to some acoustic input throughout their lifetime and all used spoken language. For this very specific patient population, we had the following hypotheses: (1) we expected to see most FC alterations in other brain regions but not the auditory network *per se,* which has never been completely deprived of its natural input (as opposed to the congenitally profoundly deaf patients, Li et al., 2016) we expected FC to be differently affected in the two patient subpopulations. Besides the existing rs-fMRI literature, these hypotheses were derived from our clinical experience, as well as our findings in a similar patient population (Wolak et al., 2017) who showed unchanged tonotopic organization (frequency representation) in the auditory cortex except for a slight enlargement of the low-frequency regions in the early-deprived group. Furthermore, as also mentioned above, there is a vast body of research showing that early sensory deficits affect brain function differently than the acquired ones which is related to the existence of sensitive periods in development (although the most tested populations were either completely deaf or completely blind) (Kral and ODonoghue, 2010; Wan et al., 2010; Desgent and Ptito, 2012; Kupers and Ptito, 2014; Slimani et al., 2014; Friedmann and Rusou, 2015; Wong et al., 2015; Kral et al., 2017).

MATERIALS AND METHODS

Subjects

The study was approved by the Medical Ethics Committee of the Institute of Physiology and Pathology of Hearing (IPPH) in Kajetany/Warsaw, Poland. Participants gave their written informed consent prior to the study and received no monetary reward for their participation. Twenty patients (11F, 9M; age 34.9 ± 8.2 years, range: 16.25–47.50 years) were recruited from the Institute of Physiology and Pathology of Hearing. Ten patients had higher (university degree), eight medium (high-school) and two basic (primary school) education. All patients had idiopathic sloping sensorineural hearing loss (partial deafness, Skarzynski et al., 2010). Ten patients had prelingual HL (diagnosed before the age of 3 years; PRE) and 10 acquired it above the age of 7 years (postlingually; POST). The mean age of the PRE group was (32.3 ± 9.4 years; age range: 16.25–42.30) and of the POST group was (37.6 ± 6.2 years; age range: 26.92–47.50) [Mann Whitney *U* test; $z = -1.32$; $p = 0.19$] and involved fewer women ($N = 3$) than the POST group ($N = 8$) [$Chi^2 = 5$; $p = 0.025$]. All subjects were right-handed. The control group included 12 women and 9 men, aged 31.8 ± 7.2 years and was matched for education levels (8 medium, 13 higher). All subjects in the control group had normal hearing (<25 dB for 0.125–8 kHz) and no tinnitus. Please see further details of participants in **Table 1**.

Audiometric Evaluation

A comprehensive audiometric evaluation was performed for each subject, both patients and the normal hearing individuals (NH) controls. The average pure tone audiometry for the whole group of patients for frequency ranges from 500 Hz to 2000 Hz (PTA) was 56.3 ± 24.3 dB for the left ear and 59.8 ± 24.4 dB for the right ear (see the audiogram for all frequency ranges in **Figure 1**). Word Recognition Scores (WRSs) were also obtained, with the Polish Monosyllabic Pruszewicz test (Pruszewicz et al., 1999) (speech presented at 65 dB) and were on the average 49 ± 38% and 44 ± 34% for the right and the left ear, respectively. The higher the score, the more words the patient was able to understand. All patients used spoken language supported with lip-reading to communicate. The PTA and the WRS scores for the PRE and the POST group were 66 ± 21 dB and 11 ± 14%, 58 ± 18 dB and 75 ± 17%, respectively. WRSs were statistically different between groups (Man Whitney *U* test, $z = -3.77$; $p = 0.000$).

TABLE 1 | Demographic and audiological data of the patient group.

No	Sex	Age (years)	Onset of SNHL	Duration of SNHL (years)	Tinnitus 0–no 1–yes	Hearing aids 0–none 1–one 2–two
1	M	31	PRE	–	0	1
2	F	37.5	PRE	–	0	2
3	F	30.3	PRE	–	0	2
4	F	41.9	PRE	–	0	0
5	M	26.92	PRE	–	0	0
6	F	31.08	PRE	–	0	0
7	M	17.25	PRE	–	0	1
8	M	42.3	PRE	–	1	0
9	M	36.8	PRE	–	1	2
10	M	36.6	PRE	–	1	2
11	F	45.25	POST	18	0	0
12	F	42.17	POST	22	0	0
13	M	16.25	POST	3	0	2
14	F	37.25	POST	8	0	0
15	F	32.9	POST	28	1	0
16	M	32.17	POST	14	1	0
17	F	42.17	POST	6	1	0
18	M	47.5	POST	19	1	1
19	F	37.5	POST	9	1	1
20	M	34.7	POST	19	1	2

Psychological Evaluation

All subjects took part in a professional psychological interview to make sure that they would be able to participate in the study. As the applied psychological tools were described elsewhere in detail (see section "Materials and Methods" in Cieśla et al., 2016), they are only briefly mentioned here. Polish versions of two screening tools, the beck depression inventory (BDI) and the state-trait-anxiety-inventory (STAI) were used to assess depressive and anxiety symptoms in study participants. BDI is a self-report inventory with 21 multiple-choice items to be responded to on a 0–3 point scale (the maximum total is 63 points) (Zawadzki et al., 2009). The STAI form X has 40 questions, with 20 questions measuring anxiety as a *state* and 20 referring to levels of anxiety as a personal *trait*. The participant responds him/herself on a 4-point Likert-type scale and the maximum total score is 80

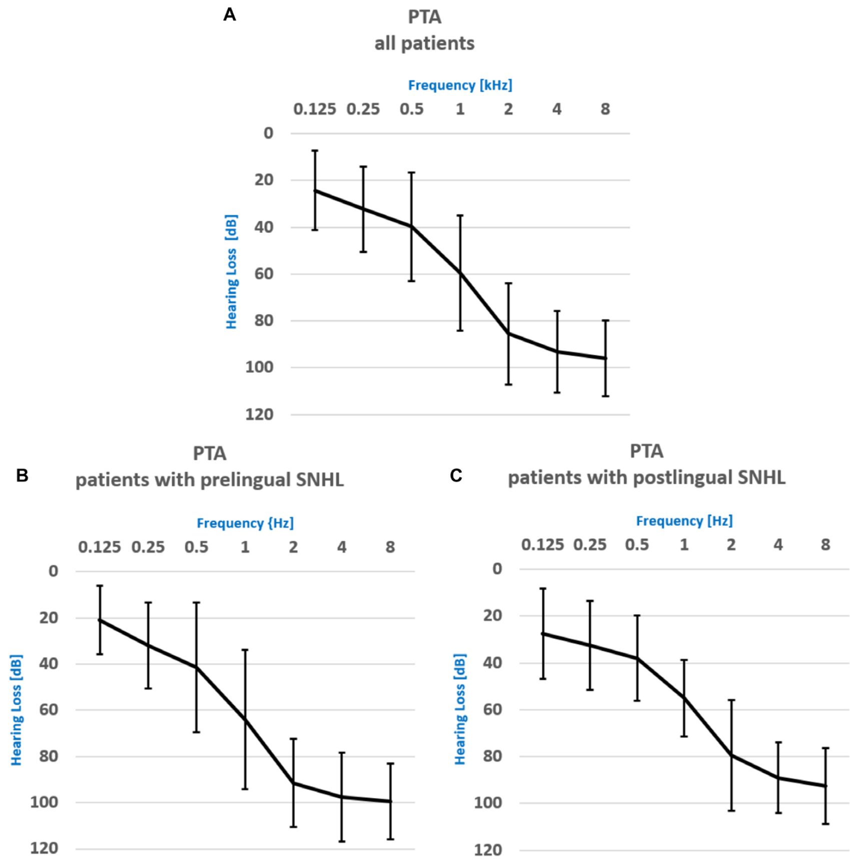

FIGURE 1 | Pure Tone Audiometry results for **(A)** the whole patient group, **(B)** the patient group with prelingual onset of SNHL, **(C)** the patient group with postlingual onset of SNHL.

(Wrześniewski, 2011). With both questionnaires, higher scores indicate more severe symptoms.

Rs-fMRI Data Acquisition

RS-fMRI data were acquired at the Biomedical Imaging Center of IPPH in Kajetany/Warsaw, Poland. RS-fMRI examination was conducted using a 3T Siemens TRIO TIM scanner equipped with a 12-channel head matrix coil. The parameters of the EPI sequence were the following: time of repetition (TR) = 2000 [ms]; time of echo (TE) = 30 [ms]; flip angle (FA) = 90°; voxel size = 3 × 3 × 3 mm; imaging matrix = 64 × 64; no of slices = 41; time of acquisition (TA) = 8.08 min; 250 data points. Participants were instructed to relax during scanning with their eyes closed and not to think of anything in particular. A structural T1 MR sequence had the following parameters: TR = 1900 [ms]; TE = 2.26 [ms]; time of inversion (TI) = 900 [ms]; flip angle (FA) = 9°; field of view (FOV) = 28.8 × 27.0 [cm]; matrix = 320 × 300; voxel size = 0.9 × 0.9 × 0.9 [mm]; pixel bandwidth = 200 Hz/pix; no of slices = 208; TA = 5:11 min.

Data Pre-processing

A standard preprocessing pipeline was applied in CONN (Connectivity Toolbox) which uses functions from Statistical Parametric Mapping 12 (SPM12) software[1]. Preprocessing of the functional data included slice timing correction, motion correction, scrubbing, linear detrending, band-pass filtering (0.01 Hz < f < 0.1 Hz), co-registration to individual T1 structural scans, spatial normalization to MNI space, and spatial smoothing (6 mm Gaussian kernel). Each subject's structural scan was segmented into gray matter, white matter, and cerebrospinal fluid (CSF) tissue classes using the unified segmentation approach implemented in SPM12. In addition, the Artifact Detection Tool[2] was used to measure motion artifacts in all individuals. Linear regression of confounding effects was applied including: mean signal from white matter and CSF, motion parameters obtained in the realignment step, volumes that showed movement exceeding 0.5mm from the scrubbing step (in the ART toolbox with conservative settings, 95th percentile in a normative sample) and 10 first scans (effect of rest). It was found that the mean frame-wise displacement (±SD) was: 0.112 ± 0.038 mm in the NH and 0.128 ± 0.056 mm in patients with SNHL (groups were not different in that aspect, p = 0.283). Seven individual volumes required scrubbing (both groups together).

[1] http://www.fil.ion.ucl.ac.uk/spm/
[2] https://www.nitrc.org/projects/artifact_detect

Statistical Analysis

All subsequent analysis of rs-fMRI outcomes was performed in CONN-fMRI FC toolbox ver. 17f[3]. The first-level whole-brain seed-driven FC maps were obtained by estimating temporal correlations of BOLD signal in seeds corresponding to nodes of canonical RSN. In addition, we used nodes corresponding to the Heschl gyri obtained from the new default atlas (132 ROIs) combining the FSL Harvard-Oxford atlas cortical and subcortical areas and the AAL atlas cerebellar areas. The analysis was performed separately for each node (the list and coordinates of all seeds is presented in **Supplementary Table S1**) and for both the patient and the normal hearing group.

For the patient group, to measure bivariate correlations between the connectivity strength and patients' audiological scores, including WRS and PTA, seed-to-voxel correlation coefficients (Pearson's R correlation coefficients) were computed and converted to normally distributed z-scores using Fisher's transform. We used WRS and PTA as covariates in the same model as they were not correlated with one another (Kendall's tau, $p = 0.49$). Since the hearing loss severity and speech understanding scores were comparable for both ears in all participants, averaged binaural PTA and WRS were used for the correlation analysis.

A second-level random effects analysis was then applied to create within-group statistical parametric maps (SPMs) for each RS network and to examine connectivity differences between groups, i.e., between the normal hearing subjects and patients, as well as between patient groups with prelingual onset of SNHL and postlingual onset of SNHL. In addition, we performed a comparison analysis between patients with tinnitus and without tinnitus, as well as with and without hearing aids. This was also done due to the fact that the proportion of patients with and without tinnitus/hearing aids was different in the PRE and the POST subgroup. For all these comparisons mean binaural PTA and WRS values were used as covariates. SPMs were generated for each outcome and thresholded at the voxel level at $p < 0.001$ uncorrected and then the cluster-size FWE-corrected level of $p < 0.05$ and with the Holm–Bonferroni method at $p < 0.05$ to account for the effect of comparisons between multiple networks and regions (Holm, 1979).

The outcomes of psychological questionnaires (STAI, BDI) were analyzed with SPSS ver. 20 software.

RESULTS

Psychological Questionnaires

The normal hearing and the patient group were not different in terms of their scores in BDI (Patients: 8.5 ± 7.2 points; NH group: 5 ± 5 points) and STAI (Patients: *anxiety as state* 32 ± 7.7 and *anxiety as trait* 32.4 ± 7.4; NH group: *anxiety as trait* 28.1 ± 5.5 and *anxiety as trait* 29.5 ± 6.2) ($p > 0.05$). In both groups the symptoms indicated non-existent or only mild depressive and anxiety symptoms.

[3]http://www.nitrc.org/projects/conn

Rs-fMRI Data

Brain-Behavior Relationship

Tables 2, **3** present RS functional connections that were found correlated with audiological scores (PTA, WRS) in the whole patient group (thresholded at the cluster-size FWE-corrected level of $p < 0.05$ and Holm–Bonferroni level at $p < 0.05$ to account for multiple comparisons of FCs). All functional connections that were found correlated with PTA and WRS values at FWEc < 0.05 but failed to exceed the Holm–Bonferroni $p < 0.05$ threshold are presented in **Supplementary Tables S2a,b**.

Hearing severity (binaural PTA) was found positively correlated with FC between the visual medial seed and bilateral occipital poles, as well as the left frontal eye field and the precuneus. At the same time, negative correlations (the less hearing loss severity the more functional coupling) between the superior node of the sensorimotor network and the occipital fusiform gyrus, as well as the right superior temporal gyrus of the language network and the DMN prefrontal hub to postcentral gyrus left and precentral gyrus right, respectively.

The only statistically significant correlation that was found for binaural WRS values in patients was a positive one between the left Heschl gyrus and bilateral lingual/intracalcarine cortex.

Subjects With SNHL vs. Normal Hearing Individuals

Second-level analysis revealed stronger FC between left Heschl gyrus and right lingual gyrus in NH, compared to the whole group of patients with SNHL (thresholded at the cluster-size FWE-corrected level of $p < 0.05$ and Holm–Bonferroni corrected at $p < 0.05$). The reverse comparison showed decreased FC in the normal hearing group between bilateral inferior parietal sulci, and bilateral precentral gyri. With this stringent statistical approach there were no other functional connections that showed significant between-group differences (**Figures 2**, **3** and **Tables 4**, **5**). All networks and seeds tested in this comparison are listed in **Supplementary Table S1**. All functional connections that were found different between the groups at FWE_c cluster size corrected threshold of $p < 0.05$ but failed to exceed the Holm–Bonferroni $p < 0.05$ correction are presented in **Supplementary Tables S3a,b**.

Patients With Prelingual vs. Postlingual Onset of Snhl

Figures 4, **5** and **Tables 6**, **7** depict differences in FC between subpopulations of patients with early *vs.* late onset of SNHL. In short, the analysis showed that subjects with prelingual SNHL exhibit a pattern of increased connectivity within the following canonical RS networks: salience, FPN, DMN, cerebellar, DAN, and visual. In the visual network, specifically, subjects with prelingual SNHL onset demonstrated increased connectivity between the medial visual seed and the occipital pole bilaterally, as well as between lateral visual cortex and left precentral gyrus. At the same time patients with postlingual onset of their hearing loss

TABLE 2 | Functional connections found correlated with binaural PTA scores in the whole patient group.

	RS network and seed region	Main anatomical region in the target region	Size of the target region in voxels (2 × 2 × 2 mm)	MNI coordinates of the target region (X,Y,Z)	p-value FWE$_c$ $p < 0.05$ corr. and Holm–Bonferroni $p < 0.05$ corr.	Direction of correlation
1.	Visual medial	Occipital pole L	170	−14, −102, −10	0.000103	positive
2.	Visual medial	Occipital pole R	128	16, −106, 0	0.001014	positive
3.	Dorsal attention FEF L	Precuneus	144	−6, −68, 32	0.000369	positive
4.	Sensorimotor sup.	Occipital Fusiform Gyrus L	113	−36, −80, −14	0.004052	negative
5.	Language pSTG R	Postcentral Gyrus Left	107	−12, −40, 54	0.003978	negative
6.	DMN MPFC	Precentral Gyrus R	106	60, −6, 28	0.005222	negative

FEF, frontal eye fields; Sup, superior; pSTG, posterior superior temporal gyrus; DMN, default mode network; MPFC, medial prefrontal cortex; L, left;, R, right.

TABLE 3 | Functional connections found correlated with binaural WRS scores in the whole patient group.

	RS network and seed region	Main anatomical region in the target region	Size of the target region in voxels (2 × 2 × 2 mm)	MNI coordinates of the target region (X,Y,Z)	p-value FWE$_c$ $p < 0.05$ corr. and Holm–Bonferroni $p < 0.05$ corr.	Direction of correlation
1.	Heschl Gyrus L	Lingual Gyrus/Intracalcarine Cortex L/R	134	4, −78, 0	0.000676	positive

L, left; R, right.

showed increased connectivity in DAN and SN, as well as some visual areas.

Supplementary Table S1 depicts all tested networks and seed regions that were used for comparisons between outcomes in patients with early vs. late onset of SNHL. **Supplementary Tables S4a,b** show all FCs that were found different between patient subpopulations at threshold of FWE$_c$ $p < 0.05$ but failed to exceed the Holm–Bonferroni $p < 0.05$ correction.

Outcomes of the comparison analysis between patients with and without tinnitus, as well as with and without hearing aids were presented in **Supplementary Tables S5a–S6b**. None of the detected connectivity differences overlapped with those detected between patients with prelingual vs. postlingual onset of hearing loss.

DISCUSSION

In the current study we investigated brain resting-state connectivity in patients with sloping sensorineural hearing loss. We found that a number of functional connections were modulated by the audiological scores presented by the patients, including their hearing loss severity and speech recognition scores. Furthermore, in a comparison analysis, significant effects were demonstrated between patients with an early onset of

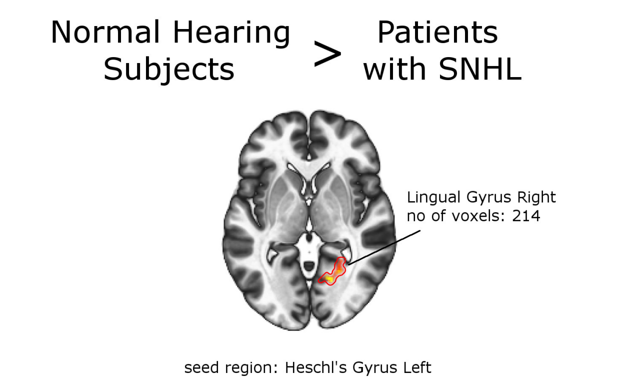

FIGURE 2 | Between-group effects. Increased functional connectivity in normal hearing subjects, compared to the group of patients as a whole. Networks and seed regions are indicated below each slice. The target regions of altered FC are outlined in red for better visualization. The number of voxels is the size of the whole target region, and the name indicates the anatomical area the majority of the voxels belonged to. If the brain side of the target region is not stated, it was in both hemispheres.

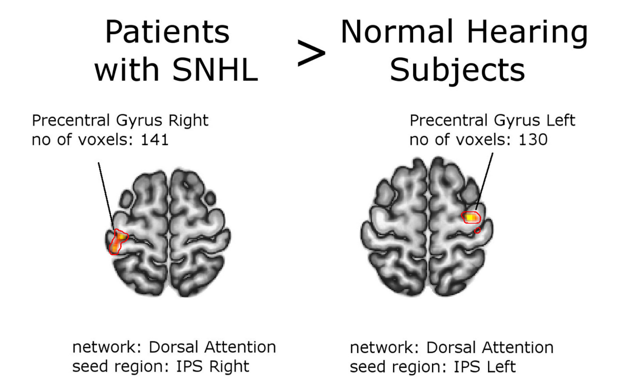

FIGURE 3 | Between-group effects. Increased functional connectivity in the group of patients as a whole, compared to normal hearing subjects. Networks and seed regions are indicated below each slice. The target regions of altered FC are outlined in red for better visualization. The number of voxels is the size of the whole target region, and the name indicates the anatomical area the majority of the voxels belonged to. If the brain side of the target region is not stated, it was found in both hemispheres.

TABLE 4 | Increased functional connectivity in Normal Hearing Subjects vs. Patients with SNHL (with PTA and WRS values used as regressors).

	RS network and seed region	Main anatomical region in the target region	Size of the target region in voxels (2 × 2 × 2 mm)	MNI coordinates of the target region (X,Y,Z)			*p*-value FWE$_c$ $p < 0.05$ corr. and Holm–Bonferroni $p < 0.05$ corr.
1.	Heschl Gyrus L	Lingual Gyrus R	214	16,	−64,	0	0.000020

L, left; R, right.

TABLE 5 | Increased functional connectivity in Patients with SNHL vs. Normal Hearing Subjects (with PTA and WRS valuesused as regressors).

	RS network and seed region	Main anatomical region in the target region (L, left; R, right)	Size of the target region in voxels (2 × 2 × 2 mm)	MNI coordinates of the target region (X,Y,Z)			*p*-value FWE$_{rmc}$ $p < 0.05$ corr. and Holm–Bonferroni $p < 0.05$ corr.
1.	Dorsal attention IPS R	Precentral Gyrus R	141	32,	−14,	62	0.001142
2.	Dorsal attention IPS L	Precentral Gyrus L	130	−38,	−26,	66	0.001859

IPS, intra parietal sulcus; L, left; R, right.

SNHL (prelingual) and those who acquired their HL later in life (postlingual). We found differences in both directions, but mostly increased functional couplings in the patient group with early auditory deficits. These results are very interesting as they may reflect the neuronal effects of the onset of a partial hearing impairment *per se*. Meanwhile, both patient subpopulations did experience some degraded auditory input, but just until different moments in their lifetime. As patients with prelingual onset of SNHL and those with postlingual onset of SNHL included different proportion of those who experienced tinnitus and/or wore hearing aids, we also checked how the two latter factors affect FC. We found no connectivity differences that could be attributed to both the onset of SNHL and tinnitus/using hearing aids. In all analyses comparing subpopulations of patients we accounted for the variance in FC related to the severity of hearing loss and speech understanding scores, in order not to confound the results. Furthermore, patient subgroups were matched for sex, as well as age for the representation of patients with tinnitus. Interestingly, against our expectations, the analysis of RSNs revealed a significant effect involving the auditory network, and namely an increase in FC in the normal hearing subjects, as compared to the patient group as a whole, between early auditory and early visual cortices.

Increased Functional Connectivity in Patients With Prelingual SNHL

We found in patients with prelingual SNHL increased functional couplings both in long-ranging brain networks, such as the DMN, the FPN and the DAN, as well as in local sensory networks, i.e., the visual areas and the sensorimotor areas. We saw that most of the FC alterations involved ipsilateral connections (*vs.* cross-hemisphere), with the effect present more often in the right brain hemisphere. We suggest in this patient population a mechanism of top-down modulation by the FPN axis. This mechanism serves to obtain optimal integration of inputs, including aspects of speech, coming from multiple sensory modalities.

In the current study we found in patients with an early (partial) auditory deprivation enhanced intrinsic FC within the visual network – including a number of early and association visual subregions. This effect was accompanied by more functional couplings from multisensory brain regions, such as the SMG (underlying visuo-tactile integration) and AG (underlying audio-visual integration) in inferior parietal cortex, and the inferior temporal gyrus (ITG). The ITG is, among other functions, involved in recognizing visual patterns, also those with linguistic features (Ardila et al., 2015). These findings point to possible multisensory compensation mechanisms occurring in the early auditory deprived brain. Indeed, there are many studies demonstrating that especially patients with early sensory deficits, both visual and auditory, rely more on multisensory experiences than the healthy population. It has even been shown that deprived sensory regions, such as the auditory cortex in congenital profound deafness, can engage in the analysis of inputs coming from other modalities (see, e.g., Karns et al., 2012 for touch and Vachon et al., 2013 for vision) or high-order functions, such as processing language (Bavelier et al., 2006; Campbell et al., 2007; Xia et al., 2017). In the current experiment we do not claim that auditory cortex became involved in processing of inputs from other modalities because we did not find enhanced connectivity between the auditory network and other sensory or association brain regions.

We suggest that the demonstrated enhanced collaboration between the multisensory and "unisensory" brain areas in this specific hearing impaired population reflects, (a) processing of vibrotactile and spatial aspects of acoustic signal, such as people's gestures or music-induced vibration, (b) experience with lip-reading and face feature analysis, (c) enhanced sensory-motor-visual integration (Verger et al., 2017; Xie et al., 2019). The latter is suggested in some animal works, which report increased input to sensorimotor areas and more sensorimotor-auditory integration after cochlear damage (Hofmeier et al., 2018; Xu et al., 2019b). We can, therefore, speculate that an early onset of HL requires more reliance

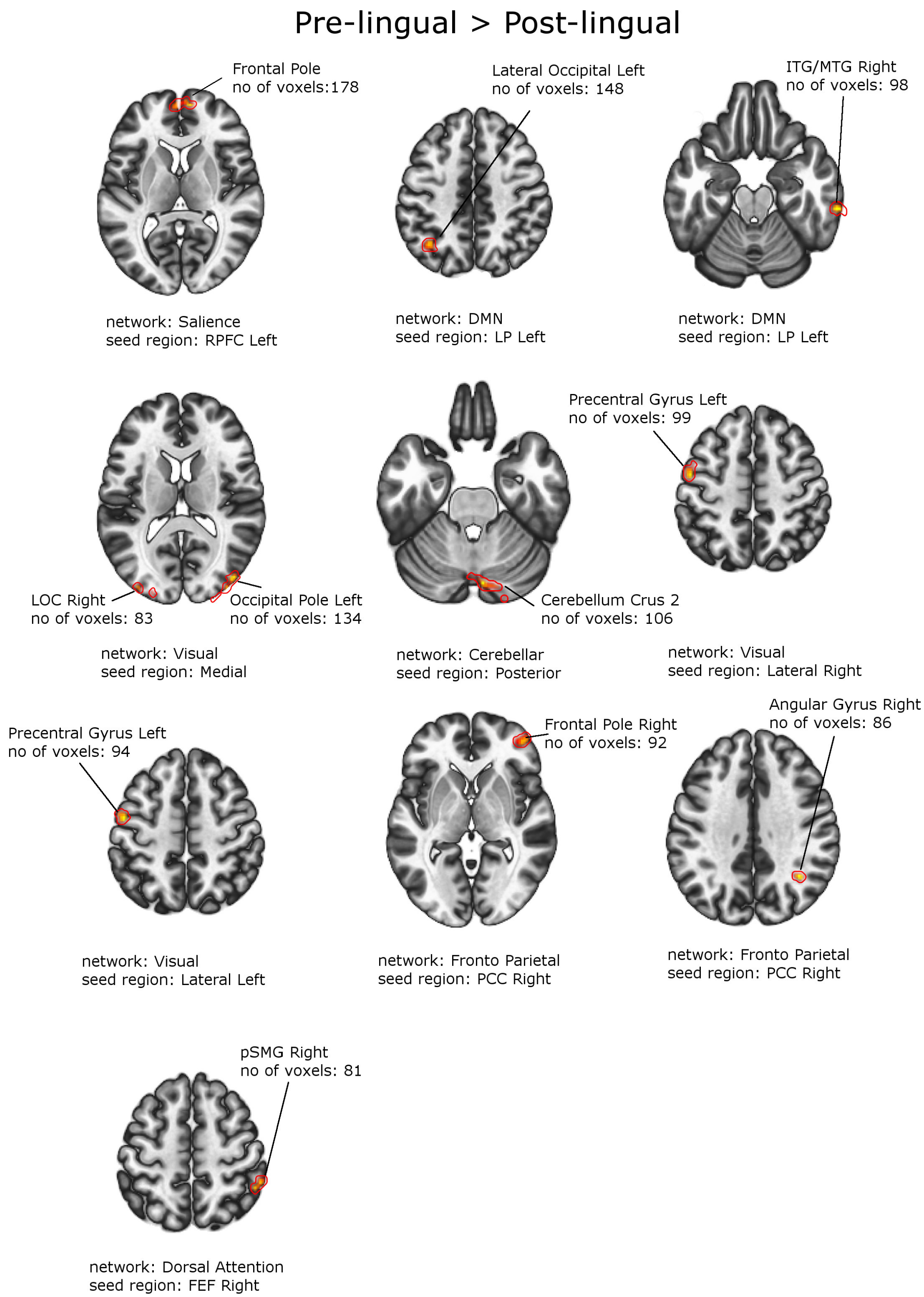

FIGURE 4 | Between-group effects. Increased functional connectivity in patients with Prelingual SNHL vs. Postlingual SNHL. Networks and seed regions are indicated below each slice. The target regions of altered FC are outlined in red for better visualization. The number of voxels is the size of the whole target region, and the name indicates the anatomical area that the majority of the voxels belonged to. If the brain side of the target region is not stated, it was found in both hemispheres.

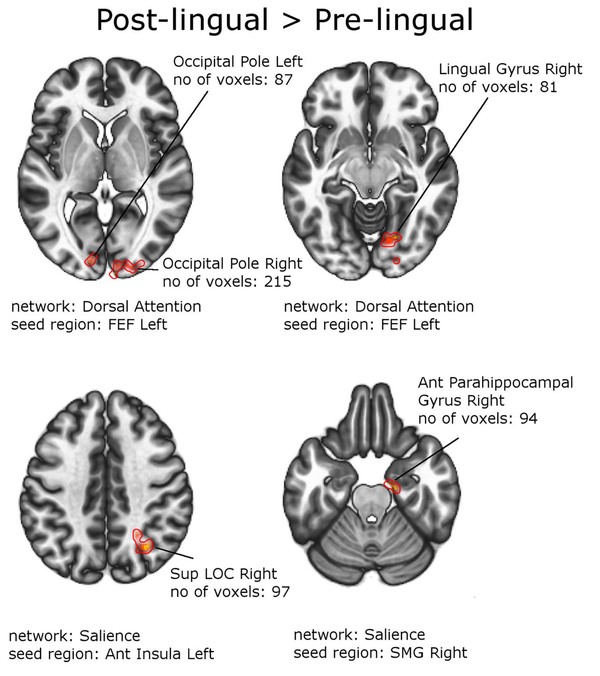

FIGURE 5 | Between-group effects. Increased functional connectivity in patients with Postlingual SNHL vs. Prelingual SNHL. Networks and seed regions are indicated below each slice. The target regions of altered FC are outlined in red for better visualization. The number of voxels is the size of the whole target region, and the name indicates the anatomical area the majority of the voxels belonged to. If the brain side of the target region is not stated, it was in found both hemispheres.

on motor and visual aspects of speech but also maybe monitoring of one's own speech which is more challenging due to the limited auditory feedback (Bavelier et al., 2006; Xia et al., 2017; Xu et al., 2019b). From our clinical experience we can confirm that early auditory deprivation affects speech production, in terms of features, such as voicing and articulation, as well as the rhythm, even if only partially (Szkielkowska et al., 2000).

In the PRE patients we also saw bilateral frontal poles having increased FC with dorsolateral prefrontal cortex. The latter is one of the main hubs of the SN, which serves environment monitoring and information integration. Frontal pole, due to its dense structural connectivity with many cortical and subcortical brain regions, has been proposed to participate in the highest level of unification of information coming from all sensory systems, as well as in processes such as attention and memory, decision making, novelty detection and multiple-task coordination (Powell and Voeller, 2004; Hartogsveld et al., 2018). We also found, in patients whose hearing abilities degraded early in their lifetime, increased FC between frontal brain regions (frontal poles, frontal eye fields) and parietal brain regions, including PCC, supramarginal (SMG) and angular gyri (AG). Both SMG and AG have been demonstrated in a number of tasks engaging control processing and shifting of attention (see Dye and Hauser, 2014 for a review).

We suggest the following underpinnings of all the described effects; In patients with a prelingual onset of SNHL, the incoming auditory input, including speech, is degraded from the very early stages of life and thus requires increased effort and attention to understand (Rosemann and Thiel, 2019). At the same time, the available cognitive resources nare limited and, thus, they need to converge on trying to decipher the incoming acoustic inputs. Meanwhile, the environment constantly provides multiple competing stimuli that can act as distractors (Knudsen, 2007). Indeed, it has been shown that patients with hearing loss use more frontal and parietal cortices when performing auditory tasks (Husain et al., 2014), with the FPN axis suggested to be involved in cognitive aspects of auditory processing (Chen et al., 2017). As in normal hearing subjects, cognitive control is probably executed by the same largely non-overlapping brain networks in the hearing-impaired individuals, including the SN as well as the FPN network (Luan et al., 2019b).

In addition, the cerebellum was more intrinsically interconnected in the PRE patient population. The cerebellum is now recognized to play a major role in sensorimotor and cognitive processes, such as phonological fluency, semantic word association and even metalinguistic skills (De Smet et al., 2013; Xu et al., 2019b). There exist both feedforward and feedback connections between the cerebellum and the cerebrum, including the auditory structures, which suggests the possible modulatory effect of the cerebellum both at the level of subcortical as well as on the cortical stages of information processing (Chen et al., 2016; Feng et al., 2018).

In sum we suggest that the control mechanisms described above, involving the FPN axis and maybe the cerebellum as well, serve to optimize integration of multisensory (visual and somatosensory) aspects of the incoming stimulation, with the degraded auditory input or regardless of it (we saw no changes in the auditory network).

Increased Functional Connectivity in Patients With Postlingual SNHL

Patients with acquired hearing deficits, in turn, revealed more functional couplings between various visual subregions and the frontal node of the DAN (with early visual regions) – the frontal eye field, as well as in the SN (with higher visual regions). In this subpopulation the effects were relatively balanced in terms of the left and right hemisphere as well as ipsi- vs. contra-lateral changes in FC. These outcomes suggest that some specific functional changes in neuronal processing might accompany postlingual partial hearing deficits, which are slightly distinct to those that might characterize patients with early hearing loss onset.

The role of the frontal eye field (FEF), which is on the border with the motor-related precentral gyrus, is control of visual attention and eye movement. Interestingly, it has been shown that FEF is densely and reciprocally structurally connected with the visual cortex (Schall, 2009). Whether, the increased FC in the current study between FEF and multiple visual

TABLE 6 | Increased functional connectivity in patients with prelingual onset of SNHL, compared to patients with postlingual onset of SNHL (with PTA and WRS values used as regressors).

	RS network and seed region	Main anatomical region in the target region	Size of the target region in voxels (2 × 2 × 2 mm)	MNI coordinates of the target region (X,Y,Z)			*p*-value FWE$_c$ $p < 0.05$ corr. and Holm–Bonferroni $p < 0.05$ corr.
1.	Salience RPFC L	Frontal pole L/R	178	8,	60,	8	0.000029
2.	DMN	Lateral Occipital L	148	−38,	−60,	46	0.000151
	LP L	ITG/MTG R	98	64,	−30,	−22	0.003416
3.	Visual	Occipital Pole L	134	−22,	−98,	28	0.000251
	Medial	LOC R	83	44,	−82,	14	0.007649
4.	Celebellar posterior	Cerebellum Crus 2	106	6,	−78,	−28	0.001823
5.	Visual lateral R	Precentral Gyrus L	99	−50,	−8,	52	0.002987
6.	Visual lateral L	Precentral Gyrus L	94	−50,	−6,	52	0.004205
7.	Fronto parietal PCC R	Frontal Pole R	92	44,	50,	0	0.004536
		Angular Gyrus R	86	36,	−54,	36	0.006909
8.	Dorsal attention FEF R	pSMG R	81	50,	−46,	58	0.009263

RPFC, rostral prefrontal cortex; PCC, posterior cingulate cortex; DMN, default mode network; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; LP, lateral parietal cortex; FEF, frontal eye fields; IFG, inferior frontal gyrus, LOC, lateral occipital complex; pSMG, posterior supramarginal gyrus; OFusG, occipital fusiform gyrus; L, left; R, right.

TABLE 7 | Increased functional connectivity in the patient group with postlingual onset of SNHL, compared to patients with prelingual onset of SNHL (with PTA and WRS values used as regressors).

	RS network and seed region	Main anatomical region in the target region	Size of the target region in voxels (2 × 2 × 2 mm)	MNI coordinates of the target region (X,Y,Z)			*p*-value FWE$_c$ $p < 0.05$ corr. and Holm–Bonferroni $p < 0.05$ corr.
1.	Dorsal attention FEF L	Occipital Pole R	215	22,	−88,	−6	0.000002
		Occipital Pole L	87	−12,	−90,	−2	0.005764
3	Dorsal attention FEF L	Lingual Gyrus R	81	20,	−70,	−10	0.008903
4	Salience ant insula L	Sup LOC R	97	34,	−60,	40	0.003958
5	Salience SMG R	Ant Parahippocampal Gyrus R	94	18,	−16,	−24	0.004775

Sup LOC, superior lateral occipital complex; Ant, anterior; Sup, superior; DMN, default mode network; FEF, frontal eye fields; IFG, inferior frontal gyrus; SMG, supramarginal gyrus; L, left; R, right.

subregions reflects the existing structural connections requires further examination, with techniques such as Diffusion Tensor Imaging (DTI; Soares et al., 2013).

Besides the enhanced FEF-visual connections we also saw increased functional couplings between lateral parts of the visual network and insula, in patients with postlingual onset of SNHL. The lateral occipital cortex is a mid-level visual cortex area subserving object recognition. Interestingly, a recent study showed increased engagement of LOC in a visual verbal rhyming task in cochlear implant candidates with postlingual profound deafness (Lazard and Giraud, 2017). In addition, although traditionally viewed as a high-level visual area, LOC was found to develop strengthened FC to the auditory cortex after auditory–tactile sensory substitution training (learning to recognize shapes from sounds that describe them) (Kim and Zatorre, 2011). This outcome suggested LOC as a brain area that is actually available to all sensory systems and not only the visual one.

The tested postlingual subpopulation of patients also demonstrated increased FC between another Silence Network region, the multisensory and attention-related SMG, with the hippocampus. As cortico-hippocampal interaction was demonstrated to be implicated in successful memory formation (Ranganath et al., 2005) this finding may indicate reliance on representations of earlier completely normal hearing experience in patients who acquired a partial hearing deficit later in life.

In sum, we can speculate on the following compensatory mechanism occurring in late onset SNHL. The Silence Network (including the insula and the SMG) that was found to be more strongly internally coupled in patients with postlingual SNHL, integrates multiple internal and external stimuli (Xu et al., 2019b). An auditory deficit can affect functioning of SN as it deprives it of one crucial source of sensory inputs. This in turn affects decision making and directing attention. Indeed, anterior insula was shown to engage in top-down detection of silent events and attention, including the auditory and the visual modality (Amaral and Langers, 2015; Xu et al., 2019b). Here, we suggest that in a situation of SNHL that was acquired later in life, SN directs attention to the remaining memory traits of speech as well as the existing current visual (and maybe also tactile) aspects of speech signal. Due to the increased involvement of the FEF and a number of visual subregions, we speculate that in partial postlingual SNHL it is mainly the audio-visual multisensory integration that helps the patients engage in the environment, despite their disability.

Brain-Behavior Correlations

In the whole patient population, after we applied a very stringent statistical threshold, we found that increased severity of hearing loss correlated with increased FC strength between the left medial visual cortex and the left occipital pole. Both these regions can be considered the early visual cortex. We therefore hypothesize that subjects with more severe deafness (higher PTA) have to rely on visual information more when recognizing speech signal, as for example during lip-reading, recognizing facial expressions or gestures. Coordinates of regions that showed increased FC were almost the same as those found more connected in the patient subgroup with prelingual SNHL (vs. postlingual SNHL). This might suggest that although the PTA values in both patient populations were not statistically different, the fact that the PTA was slightly lower in the early-onset group (66 $\pm$ 21 dB in PRE vs. 58 $\pm$ 18 in POST) might have had some effect on RSN.

Another connection that was positively correlated with PTA was between FEF and precuneus, which might again imply an increased reliance on/attention to the incoming visual input in patients with partial hearing loss. At the same time, with better hearing (lower PTA values) FC was enhanced between sensorimotor brain areas (superior parietal cortex, pre- and postcentral gyri) and multisensory brain regions, including STG, PFC and higher visual cortex. This again suggests that collaboration of senses might serve as compensation for the degradation of the incoming auditory input. In addition, we saw that with increasing speech recognition scores FC between the early auditory cortex (HG) and the early visual cortex (lingual gyrus) was also enhanced. This finding of enhanced connections between early sensory cortices is indeed intriguing, as we also found that this coupling was stronger in the normal hearing population as compared to the patient group as a whole (see below). For more in-depth interpretation of these finding, due to the relatively small sample size of patients (N = 20), further investigation is essential.

Comparisons of Functional Connectivity Between Patients With SNHL and Normal Hearing Individuals

In the patient population we saw enhanced FC between bilateral IPS in the DAN and bilateral sensorimotor cortices. This internal correlation of regions underlying perceptuo-motor processing and coordination again point to the fundamental importance of multisensory processing in the hearing deprived CNS, during processes such as reading and producing gestures, as well as one's own speech production control. More interestingly, however, participants with normal hearing demonstrated enhanced collaboration between early auditory and visual seeds (see above for the same effect of increased FC accompanying increased speech understanding in the patient population). We did not hypothesize that we would see any effects in the auditory system of the tested patients as they never experienced a total auditory deprivation. experienced joint exposure. However, we speculate that in case of normal hearing what we see is the effect of the very often of early sensory cortices to auditory and visual input, both not degraded. This experience might enhance functional coupling between early sensory brain regions. In the case of patients, especially those with early developed auditory deficits, such an experience is never the case. This does not exclude, however, enhanced collaboration between higher sensory and association regions in the hearing impaired. In fact, with only partial hearing deficit the early auditory cortex is never fully deprived of auditory input.

Methodological Issues and Study Limitations

A Whole-Brain Approach

In the current study it was especially important for us to take a whole-brain approach to the analysis of RSN. At the same time, in all but few recent studies involving patients with hearing deficits (Puschmann and Thiel, 2017; Chen et al., 2018; Xie et al., 2019), the RSN analysis was limited to only several selected resting-state networks (as a whole or parts of them), mainly auditory, DMN, VAN/DAN, and SN. We understand the rationale of testing the involvement of certain pre-selected brain regions in deprivation-related functional brain changes. In the current study, however, although we put forward a hypothesis it had to be first verified, as we tested a unique patient population. In addition, in the face of the most recent studies in human and in animals, we assumed a perspective of hearing impairment as a connectome disease and, as such, something potentially related to changes in many remote brain networks (Xu et al., 2019c). The whole brain approach, however, makes the statistical thresholds more stringent (more comparisons imply more corrections for multiple comparisons). It is, therefore, possible that we might have found more differences, both between the patient population as a whole and the normal hearing subjects, as well as across patients, if we focused our analysis on a limited number of seeds and/or used a less stringent statistical approach. For completion, in the **Supplementary Materials**, we provide a list of all outcomes of the RS analysis that did not exceed the strict statistical threshold after correction for multiple comparisons between RSN/regions.

The Role of Tinnitus

We acknowledge that an estimated 30–40% of patients with SNHL also have tinnitus which can affect FC, as it was demonstrated in a number of studies (Burton et al., 2012; Schmidt et al., 2013; Chen et al., 2014, 2015; Minami et al., 2015, 2017; Leaver et al., 2016; Wei-Wei et al., 2018). Some studies also found changes in the cerebellum or between the cerebellum and the cortex in tinnitus (Chen et al., 2017; Feng et al., 2018). In our study half of the patients (N = 9) also suffered from tinnitus. We therefore cannot exclude the possibility that the presented outcomes are related to the presence of tinnitus. Indeed, we did find FC differences between patients with and without the experience of tinnitus. None of these differences overlapped with those found for comparisons between patients with early and late onset of SNHL. Studying the effect of tinnitus was not the aim of the current experiment and so we did not collect any further measures of tinnitus in individual subjects, such as tinnitus laterality, duration, severity and bothersomeness. Meanwhile, increasingly more rs-fMRI studies indicate that these parameters significantly change the way tinnitus affects brain FC

(Schmidt et al., 2013; Zhang et al., 2015; Chen et al., 2017; Feng et al., 2018). Such an endeavor should, however, be definitely undertaken in our future studies.

The Studied Sample

Finally, the relatively small sample size in the current experiment should be mentioned as a study limitation. It is definitely the case that individual variability of FC can be high and thus can significantly influence group results if the studied groups is small. In addition, half of the study participants wore one or two hearing aids, with the other half not using any kind of amplification (which can affect FC, as shown in **Supplementary Materials**). In addition, there were different proportions of patients with and without tinnitus in the PRE and POST patient subpopulation. We are planning, in our future studies, to evaluate RSNs in homogenous subgroups of patients separately, for instance involving only patients with an early or a late onset of the hearing impairment, and/or patients that have similar levels of hearing loss and/or speech performance, users and non-users of HAs, with and without tinnitus. These parameters can then be more reliably evaluated as potential factors shaping resting state FC.

CONCLUSIONS

Taken together, the results of our study indicate that both a general loss of function and compensatory plasticity likely coexist between various networks in the auditory-deprived brain. Whether or not sensory deprivation caused by SNHL might be solely attributed to disruptions in connectivity patterns is, nevertheless, yet to be determined. However, earlier partial hearing deficits definitely seem to induce increase in FC particularly, such as by the additional involvement of subregions of the visual and sensorimotor systems. In sum we propose a mechanism of top-down modulation of perceptual processing by the frontal, parietal and cerebral brain regions that supports optimal integration of incoming multisensory information. Nevertheless, further rs-MRI studies are needed to address the effects of partial hearing loss of varying severity and age at onset, on intrinsic functional networks in the brain.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was approved by the Bioethical Committee of the Institute of Physiology and Pathology of Hearing.

AUTHOR CONTRIBUTIONS

TW designed the fMRI paradigm, analyzed the fMRI data, and prepared the manuscript. KC designed the study, performed the fMRI study and psychological assessments, and prepared the manuscript. AP analyzed the fMRI data and prepared the manuscript. EW recruited the patients and performed the medical examinations. BB and HS consulted the study design and preparation of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2019.00284/full#supplementary-material

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Early-Stage Vision and Perceptual Imagery in Autism Spectrum Conditions

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Autism spectrum conditions (ASC) are characterized by multifaceted alterations in visual perception and mental imagery. However, the interaction between early-stage visual perception and imagery has not been explored. We recruited 40 individuals with ASC and 20 neurotypical control volunteers to participate in a lateral masking task. Participants detected a luminance-contrast target pattern (Gabor patch) flanked by two collinear masks. The flanking masks inhibit target detection at small target-mask distances and facilitate target detection at intermediate target-mask distances. In the perceptual task, the masks appeared adjacent to the target. In the imagery task, participants imagined the masks immediately after seeing them. Results revealed that individuals with ASC characterized by exceptional visuoconstructional abilities (enhanced Block Design performance; $n = 20$) showed weaker inhibition at small target-mask distances and stronger facilitation at intermediate target-mask distances relative to the controls. Visual imagery was markedly dampened in ASC regardless of the visuoconstructional abilities. At the behavioral level, these results indicate increased facilitation *via* lateral connections in the primary visual cortex (V1) of individuals with ASC who exhibit exceptional visuoconstructional abilities, together with less efficient mental imagery.

Keywords: autism, perception, mental imagery, early vision, lateral masking

INTRODUCTION

Autism spectrum conditions (ASC) are characterized by atypical neurodevelopmental patterns, often leading to impairments in social interactions, communication, and inflexible behavior. Additionally, perceptual anomalies are an important aspect of ASC (Dakin and Frith, 2005; Simmons et al., 2009; Mottron, 2011; Robertson and Baron-Cohen, 2017), as outlined by the weak central coherence framework (Happé and Frith, 2006) and the enhanced perceptual functioning hypothesis (Mottron et al., 2006). The core feature of these theories is the abnormal interaction between bottom-up and top-down processes (Pellicano and Burr, 2012).

During low-level (early-stage) visual perception, the sensory system automatically extracts elementary information from external objects (e.g., lightness, color, stereopsis, and motion).

Low-level vision is bottom-up and data-driven because it originates with the stimulation of rods and cones in the retina, and this information is immediately forwarded to the visual cortex *via* the lateral geniculate nucleus. In contrast, top-down processes refer to the effect of previous knowledge and mental effort on perception and recognition. In other words, the brain makes predictions and inferences based on past experiences and memories (Pellicano and Burr, 2012). A typical example is mental imagery (visualizing or "seeing in the mind's eye"), which is similar to perceptual experience, but occurs in the absence of external objects: the individual retrieves images from the memory and intentionally maintains this information in the focus of consciousness (Kosslyn et al., 2006).

A paradigm shift in the research of sensory cortical areas led to the recognition that the primary visual cortex (V1) is not a passive "blackboard" for the bottom-up perception of basic object features. It turned out that top-down signals from higher-level cortical areas (e.g., prefrontal cortex and anterior cingulate cortex) modulate neural activity even in the V1 during working memory, retrieval, and mental imagery (Pearson et al., 2015; Roelfsema and de Lange, 2016). Caron et al. (2006) showed enhanced performance in the detection of simple visual stimuli and superior discrimination of first-order gratings in ASC, which indicates a heightened functioning of V1. However, despite extensive research efforts, we behold scarce knowledge about the interaction between bottom-up and top-down processes in the earliest stage of visual information processing in ASC.

The lateral masking task provides a unique opportunity for the behavioral assessment of bottom-up perception and top-down imagery at the level of the V1 (Ishai and Sagi, 1995; Kéri, 2015; Maróthi and Kéri, 2018; **Figure 1**). In the perceptual part of the task, participants detect a central low-contrast target (Gabor patch) vertically flanked by two high-contrast masks. Gabor patches are small, bean-shaped objects consisting of alternating, brighter and darker regions, providing an optimal stimulus for the V1 (Ishai and Sagi, 1997; **Figure 1**). The luminance contrast of the target Gabor patch is defined by the difference in its brightness and that of the background. The flanking masks facilitate the detection of the central target if they fall within an intermediate distance from the target: participants are able to detect a target with low contrast. However, the masks have an inhibitory effect if the target-mask distance is small, that is, a high contrast is necessary for target detection. It has been postulated that the effect of masks can be attributed to lateral interactions between neuronal groups and their feedback modulation in the V1. These lateral (horizontal) interactions are thought to be mediated by short-range connections between neurons responding to similar visual stimuli (Polat and Sagi, 1993; Polat et al., 1998; Angelucci et al., 2002; Crook et al., 2002). Interestingly, we can observe similar masking effects when participants only imagine the previously presented masks, which indicates an interplay between bottom-up and top-down processes (Ishai and Sagi, 1995). At the neural level, cortical cells responding to simple visual stimuli and their lateral interactions might be activated by signals from higher-level extrastriate and prefrontal areas in the absence of external stimuli (Freeman et al., 2003). Moreover, the imagery-induced facilitation of target detection persists for several minutes after viewing the masks, which may point to the existence of a monocular, orientation-specific, low-level iconic memory system that stores the sensory trace of the masks and enables the reactivation of these low-level representations during top-down mental imagery (Ishai and Sagi, 1995). It has also been shown that the top-down imagery effect is weaker than the facilitation induced by the physical presence of the masks and is especially pronounced at intermediate target-mask distances (Ishai and Sagi, 1997). It must be

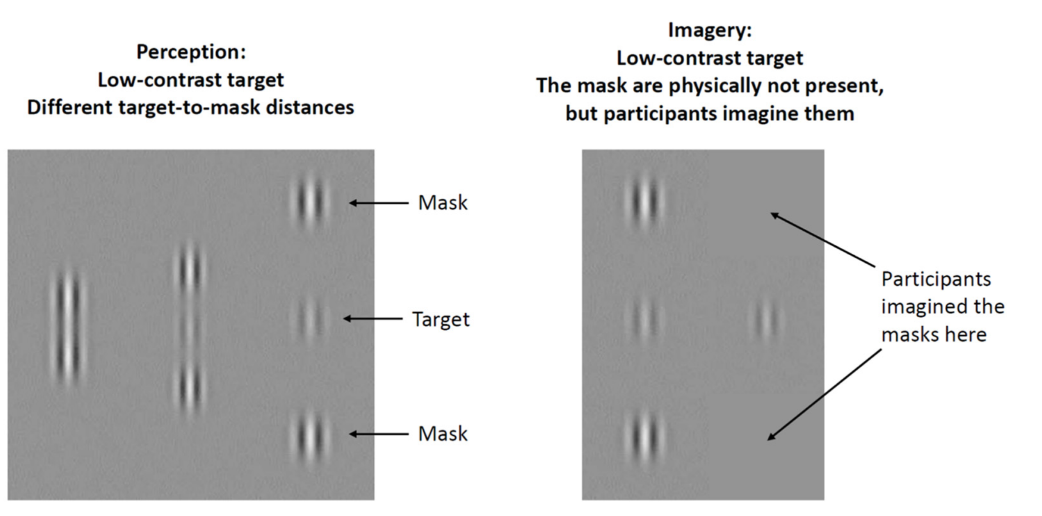

FIGURE 1 | Illustration of experimental stimuli. A low-contrast, central Gabor patch (target) was flanked by two lateral masks at three different target-mask distances (1λ, 3λ, and 6λ). Contrast threshold was measured for the target. At short target-mask distances (1λ), masks inhibit target detection (higher contrast threshold is needed for detection), at intermediate target-mask distances (3λ) masks facilitate target detection (lower contrast threshold is needed for detection), whereas at long target-mask distances (6λ) masks have a negligible effect.

underlined that higher-level top-down control during imagery is different from early-stage feedback mechanisms related to short-term memory and to the modulation of target-mask interactions (Gilbert et al., 2000; Angelucci et al., 2002; Freeman et al., 2003; Summerfield and Egner, 2009). Anatomical and physiological measurements from the macaque mapped the role of intra-areal V1 lateral connections and inter-areal feedback connections to V1 in spatial summation. Monosynaptic lateral connections within V1 mediated interactions in the spatial summation field of neurons, but feedback circuits from extrastriate cortex to V1 were needed for the full spatial range of center-surround interactions necessary for the contextual modulation and global-to-local integration of visual signals (Angelucci et al., 2002).

Kéïta et al. (2011) applied the lateral masking task to assess the functional integrity of lateral interactions in the visual cortex of individuals with ASC. The authors measured contrast thresholds for a centrally presented target Gabor patch flanked by collinear masks at different distances. As expected, both ASC and control groups showed heightened target sensitivity when the target-mask distance was intermediate. Strikingly, this facilitation was significantly greater in the ASC group relative to the control group (Kéïta et al., 2011). The authors concluded that atypical visual functions in ASC can be explained by altered lateral interactions in the visual cortex responsible for the earliest stage of feature extraction (e.g., luminance, hue, spatial frequency, and orientation of objects). However, other groups failed to replicate these findings (Jachim et al., 2015; Dickinson et al., 2018), possibly because of substantial differences in samples and psychophysical methods. There are no studies aimed to evaluate imagery in the same experimental setting.

To resolve these controversial results, it is critical to take into consideration that individuals with ASC exhibit a high degree of variation in the development of visuospatial functions (Muth et al., 2014), and it may be related to mental imagery (Soulières et al., 2011). Some of them display outstanding performances (phenotypic peaks) on tasks assessing visuoconstructional abilities (e.g., Block Design and Raven's Progressive Matrices) relative to other cognitive functions (Caron et al., 2006). The Block Design test is a part of non-verbal IQ assessment, during which participants are asked to rearrange blocks with different color patterns on their sides to match a predefined template (Wechsler, 1997). Regarding mental imagery, individuals with ASC who exhibit a Block Design peak performed better on a mental rotation task than non-autistic controls and ASC individuals with no Block Design peak. This indicates their heightened imagery ability to form, access, and manipulate mental images (Soulières et al., 2011), which is in line with the classic idea that some people with ASC think in pictures (Grandin, 1995; Kana et al., 2006; Heaton et al., 2008; Soulières et al., 2009; Sahyoun et al., 2010). However, it is not known whether enhanced visuoconstructional and imagery abilities are related to the earliest level of visual information processing, and how top-down factors interact with bottom-up perception.

Therefore, we tested the following hypotheses: (1) individuals with ASC exhibiting a Block Design peak (ASC Peak) show higher facilitation in the lateral masking task relative to neurotypical controls and ASC with no such phenotypic peak (ASC Non-Peak); and (2) based on the results of Soulières et al. (2011), we hypothesized that individuals with ASC Peak show enhanced mental imagery abilities.

MATERIALS AND METHODS

Participants

We recruited 40 individuals living with ASC and 20 neurotypical control subjects matched for sex, age, and education by contacting self-help and community support groups (**Table 1**). Individuals with Asperger's syndrome were not included. The study was conducted at the National Institute of Psychiatry and Addictions, Budapest, Hungary. For the diagnosis, we used the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) and the Autism Diagnosis Observation Schedule (ADOS-G, module 3 or 4; Lord et al., 2000). The interviews were conducted by trained clinical psychologists who were blind to the aim of the study. Individuals with neurological and psychiatric disorders other than ASC did not participate in the study. None of our volunteers received psychotropic medications. There were four sharp perceivers in the control group (visual acuity better than 20/20), and seven in the ASC group (Sloan visual acuity chart, Precision Vision, LaSalle, IL, USA; Tavassoli et al., 2011). The remaining participants had normal (20/20) visual acuity. There

TABLE 1 | Participants of the study.

	Autism spectrum disorder		Neurotypical controls	*F*	*p*
	Visuoconstructional Peak	**Non-Peak**			
Male/female	20/0	20/0	20/0	-	-
Age (years)	23.6 (6.4)	24.0 (5.9)	23.9 (7.0)	0.02	0.98
Education (years)	12.5 (4.3)	12.9 (3.6)	13.0 (5.1)	0.07	0.93
Full-scale IQ	104.2 (11.9)	102.0 (9.2)	101.5 (10.2)	0.38	0.69
Performance IQ*	112.1 (12.2)	101.8 (9.1)	100.5 (9.7)	7.44	0.001
Verbal IQ	96.4 (11.3)	102.1 (9.0)	102.7 (10.9)	2.22	0.12
Block Design values*	18.0 (4.3)	11.3 (3.0)	10.7 (2.4)	29.63	<0.001
Autism Diagnostic Interview-Revised					
Social	22.7 (5.3)	22.1 (6.7)	-	0.10	0.76
Communication	17.6 (4.9)	17.2 (4.2)	-	0.08	0.78
Behavior	6.4 (2.5)	5.9 (2.3)	-	0.43	0.51

*Data are mean (standard deviation). The table shows between-group comparisons with one-way ANOVAs. *Peak > Non-Peak = Controls ($p < 0.05$, Tukey's HSD tests).*

was no evidence of strabismus in our sample as confirmed by Hirschberg corneal reflex test.

All participants gave written informed consent, and the study was approved by the National Medical Research Council (Budapest, Hungary; ETT-TUKEB 18814). Based on the permission of the National Medical Research Council, the study was also approved by the local ethics board of the National Institute of Psychiatry and Addictions (Budapest, Hungary). All research was performed in accordance with relevant guidelines and regulations.

Classification Based on Block Design Performance

We used the Block Design subtest of the Wechsler Intelligence Scale (WAIS-III; Wechsler, 1997) to determine whether participants with ASC exhibited an outstanding visuospatial performance or not. By using the criteria of Soulières et al. (2011), a significant strength or peak (less than 5% of the general population and approximately 40%–50% of individuals with ASC) in the Block Design subtest was defined as a difference of at least 3.9 points between the standard score on the Block Design subtest and the average of all standard WAIS-III scores for a given individual. From a larger sample, we selected 20 individuals with Block Design peak (ASC Peak, Block Design score range: 4.2–7.5, three sharp perceivers), and 20 individuals without such performance strength (ASC Non-Peak, Block Design score range: −0.5 to 1.1, four sharp perceivers). The Block Design classification process was blinded.

Lateral Masking

The procedure was identical to that used in our previous studies (Kéri, 2015; Maróthi and Kéri, 2018), and here we only describe a short summary (**Figure 1**). We measured contrast threshold for a target Gabor patch when it was flanked by two lateral collinear masks with different target-to-mask distances (perception condition) or when the masks were not physically present, but the participant was instructed to imagine them (imagery condition). Target and mask Gabor patches appeared on a MultiSync PA301W monitor (NEC, Itasca, IL, USA; display area: 10° by 10°; viewing distance: 150 cm; mean display luminance: 50 cd/m^2; resolution: 10-bit), characterized by spatial frequency (6.7 cycles/degree for both target and masks), luminance-contrast (masks: 40% of Michelson-contrast), and Gaussian envelope size (0.15°). The gamma function of the screen was linearized by using a lookup table. We selected the spatial frequency of the stimuli because it provided a reliable masking effect in our previous studies (Kéri, 2015; Maróthi and Kéri, 2018).

Before the measurements, participants received a practice run to ensure that the task instructions were clear and understandable (one block of 50 trials, including perception and imagery). Each trial was initiated by the subject who pressed a key on the computer keyboard. Four subsequent phases comprised a trial: blank pre-stimulus period (500 ms), first stimulus period (90 ms), blank inter-stimulus interval (1,000 ms), and second stimulus period (90 ms). We asked the participants to indicate whether the target patch was flashed during the first or the second stimulus period by pressing two different keys ("0" or "9"). We administered nine randomized blocks of 50 trials during which the target-mask distance was constant. The center-to-center target-mask distance was depicted by the wavelength of the Gabor patched (inverse of the spatial frequency, λ): 1, 3, or 6λ. Each perception block was immediately followed by a corresponding imagery block during which participants were requested to imagine the masks at the same distance as they saw in the preceding perception block. The contrast threshold for a target without masks was measured in a separate block.

We used a staircase method, converging at 79.4% performance, to measure the target contrast threshold (Levitt, 1971). After three consecutive correct responses, the contrast was decreased by 0.1 log unit, whereas after an incorrect response, the contrast was increased by 0.1 log unit. A block was terminated after eight reversals (when contrast was lowered and subsequently increased), and the final contrast threshold was the average of the last seven reversals. The changes in the contrast threshold were expressed relative to the baseline (no mask) condition. Positive values mean that contrast detection thresholds increased in the presence of the masks, whereas negative values indicate that the detection thresholds were reduced. Contrast threshold changes were characteristically affected by the target-to-mask distance (1λ: masks inhibit target detection; 3λ: masks facilitate target detection; 6λ: masks have negligible effects on target detection; Polat and Sagi, 1993).

Fatigue and Motivation

To measure changes in mental efforts and motivation during the experiment, we used the Multidimensional Fatigue Inventory (MFI) at the beginning and at the end of the procedure. The MFI consists of 20 items defining four categories: general fatigue, mental fatigue, reduced activities, and motivation. Each item is rated on a 5-point Likert scale (from "True" to "Not true"). Lower MFI points mean greater fatigue (Smets et al., 1995; Gergelyfi et al., 2015).

Data Analysis

We used STATISTICA 13.1 software (TIBCO, Palo Alto). First, normality of data distribution and homogeneity of variance were checked with Kolmogorov–Smirnov and Levene's tests, respectively. The main dependent measure was contrast threshold changes in the lateral masking task, which was entered into analysis of variances (ANOVAs), followed by Tukey's Honestly Significant Difference (HSD) tests. In the ANOVA, the between-subjects factor was the three groups (ASC Peak, ASC Non-Peak, and controls), and the within-subjects factor was the three target-mask distances. We also explored whether facilitation and inhibition were significant at different target-mask distances by comparing the contrast threshold value at each distance with the baseline (no mask) value with *t*-tests (two-tailed, Bonferroni-corrected for multiple comparisons). Demographic parameters and IQ were compared in the three groups with one-way ANOVAs. Cohen's effect sizes were calculated for the head-to-head comparison of the groups. Pearsons's product moment correlation coefficients were determined between contrast threshold changes and Block

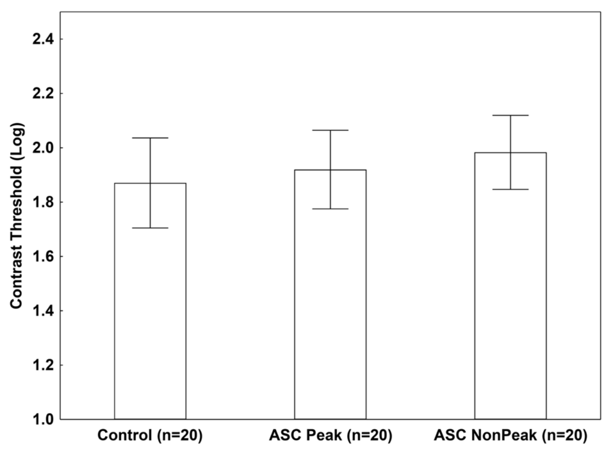

FIGURE 2 | Mean log-contrast threshold (95% confidence intervals) in people with autism spectrum conditions (ASC) exhibiting a Block Design peak performance (ASC Peak), an average Block Design performance (ASC Non-Peak), and neurotypical (non-autistic) control volunteers. In this condition, a single Gabor stimulus was presented without masks. There were no statistically significant between-group differences ($p > 0.5$).

Design scores. The level of statistical significance was set at $\alpha < 0.05$.

RESULTS

Perception

When an isolated Gabor patch was presented without masks, we found no significant difference among the groups (ASC Peak, ASC Non-Peak, and controls) in the contrast threshold ($p = 0.54$; **Figure 2**).

When the target Gabor patch was presented with masks in the perceptual task, there were significant main effects of group ($F_{(2,57)} = 20.00$, $p < 0.001$, $\eta^2 = 0.41$) and target-mask distance ($F_{(2,114)} = 567.56$, $p < 0.001$, $\eta^2 = 0.91$). The interaction between group and target-mask distance was also significant ($F_{(4,114)} = 9.60$, $p < 0.001$, $\eta^2 = 0.25$).

As shown in **Figure 3**, the contrast threshold changes were significantly lower in the ASC Peak group relative to the control individuals at 1λ (less inhibition) and 3λ [more facilitation; Tukey's HSD tests, $ps < 0.01$; d (1λ) = 1.5; d (3λ) = 1.6]. No such differences were observed when the ASC Non-Peak subjects were compared with the control group [$ps > 0.3$; d (1λ) = 0.5; d (3λ) = 0.7]. Finally, when the ASC Peak and ASC Non-Peak groups were directly compared, we found no differences at 1λ ($p = 0.29$; $d = 0.6$), whereas at 3λ the contrast threshold change was significantly lower in the ASC Peak group than in the ASC Non-Peak group ($p < 0.01$; $d = 1.7$; **Figure 3**).

We calculated the correlations between contrast threshold changes and Block Design Scores at different target-mask distances. A significant relationship was found at 3λ in the ASC Peak group (partial $r = -0.65$, $p < 0.01$; **Figure 4**).

We also investigated whether facilitation and inhibition were significant at the different target-mask distances by comparing contrast thresholds at each distance with the baseline (no mask) value. These analyses indicated significant inhibition at 1λ and facilitation at 3λ in each group (controls: 1λ: $t_{(19)} = -23.13$, $p < 0.001$, $d = 1.4$; 3λ: $t_{(19)} = 13.97$, $p < 0.001$, $d = 0.7$; ASC Peak: 1λ: $t_{(19)} = -13.15$, $p < 0.001$, $d = 1.2$; 3λ: $t_{(19)} = 9.22$, $p < 0.001$, $d = 1.1$; ASC Non-Peak: 1λ: $t_{(19)} = -14.94$, $p < 0.001$, $d = 1.6$; 3λ: $t_{(19)} = 4.75$, $p < 0.01$, $d = 0.4$). At 6λ, we found no significant facilitation in either group ($ps > 0.1$).

Imagery

In the imagery task, the main effect of group was not significant ($p = 0.56$). However, the main effect of target-mask distance ($F_{(2,114)} = 104.37$, $p < 0.001$, $\eta^2 = 0.65$) and the two-way interaction between group and target-mask distance ($F_{(4,114)} = 33.52$, $p < 0.001$, $\eta^2 = 0.54$) were significant. The *post hoc* tests indicated that the ASC Peak and ASC Non-Peak groups displayed minimal inhibition at 1λ and weak facilitation at 3λ as compared with the controls [$ps < 0.01$; ASC Peak vs. controls: d (1λ) = 1.4; d (3λ) = 2.3; ASC Non Peak vs. controls: d (1λ) = 0.9; d (3λ) = 1.6]. There were no significant differences between individuals with ASC Peak and ASC Non-Peak [$ps > 0.5$; d (1λ) = 0.4; d (3λ) = 0.3; **Figure 3**].

When facilitation and inhibition were investigated at the different imagined target-mask distances by comparing contrast thresholds at each imagined distance with the baseline (no imagined mask) value, significant effects were found in the control group at 1λ ($t_{(19)} = -7.57$, $p < 0.01$, $d = 0.5$), at 3λ ($t_{(19)} = 8.02$, $p < 0.01$, $d = 0.5$), but not at 6λ ($p > 0.1$). In the ASC groups, there were no similar effects ($ps > 0.1$).

Fatigue and Motivation

Individuals with ASC and healthy control subjects exhibited statistically similar scores on the MFI (before the experiment: ASC Peak: 37.4 ($SD = 4.9$), ASC Non-Peak: 38.3 ($SD = 5.1$), controls: 36.9 ($SD = 4.6$); after the experiment: ASC Peak: 36.3 ($SD = 5.0$), ASC Non-Peak: 38.0 ($SD = 5.2$), controls: 36.0 ($SD = 4.7$); ANOVA main effects of group and assessment time: $ps > 0.5$). The MFI scores did not correlate with perception, imagery, and neuropsychological performances ($ps > 0.5$).

DISCUSSION

The results from the control group are in keeping with the findings of prior experiments (Polat and Sagi, 1993). However, we only found partial support for our hypotheses in ASC. In accordance with the results of Kéïta et al. (2011), we observed higher facilitation of contrast detection in ASC relative to the controls when the target-mask distance was intermediate (3λ). However, this effect was confined to the ASC Peak group. In addition, Block Design performances specifically correlated with lateral facilitation in the ASC Peak group. This suggests that altered developmental trajectories, leading to outstanding higher-level visuoconstructional abilities, may also result in the enhancement (less inhibition) of lateral connections in the V1. From another point of view, atypical higher-level perception may stem from altered low-level processes in ASC (Perreault et al., 2015). Vandenbroucke et al. (2008) used an electrophysiological

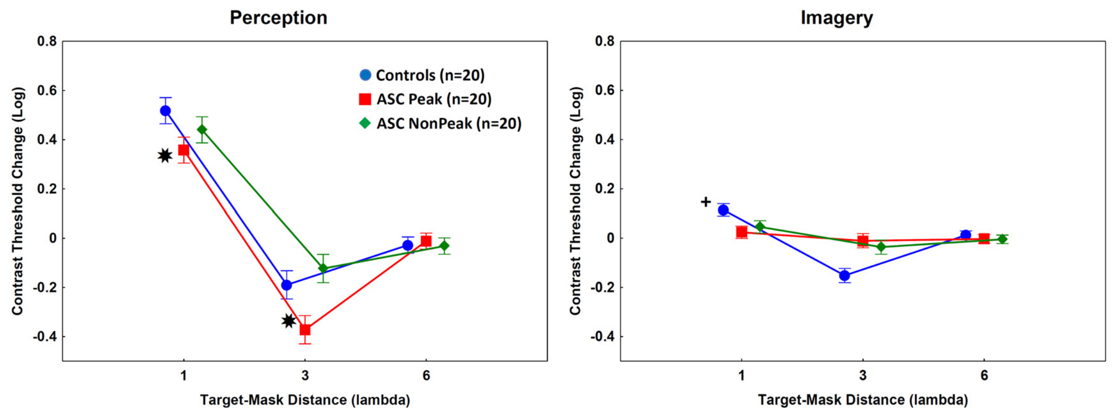

FIGURE 3 | Mean log-contrast threshold changes (masks present minus isolated target stimuli). Error bars denote 95% confidence intervals. Negative values indicate facilitation by masks (lower contrast threshold for the target when the masks are presented relative to an isolated target). Perception: *Contrast threshold changes were significantly lower in the ASC Peak group (people with ASC exhibiting a Block Design peak performance) relative to the control individuals at 1λ and 3λ [Tukey's Honestly Significant Difference (HSD) tests, *ps* < 0.01]. Imagery: +The ASC Peak and ASC Non-Peak (people with autism spectrum disorders exhibiting an average Block Design performance) groups showed weaker inhibition at 1λ (lower contrast threshold changes) and weaker facilitation (higher contrast threshold changes) at 3λ relative to the controls (Tukey's HSD tests, *ps* < 0.01).

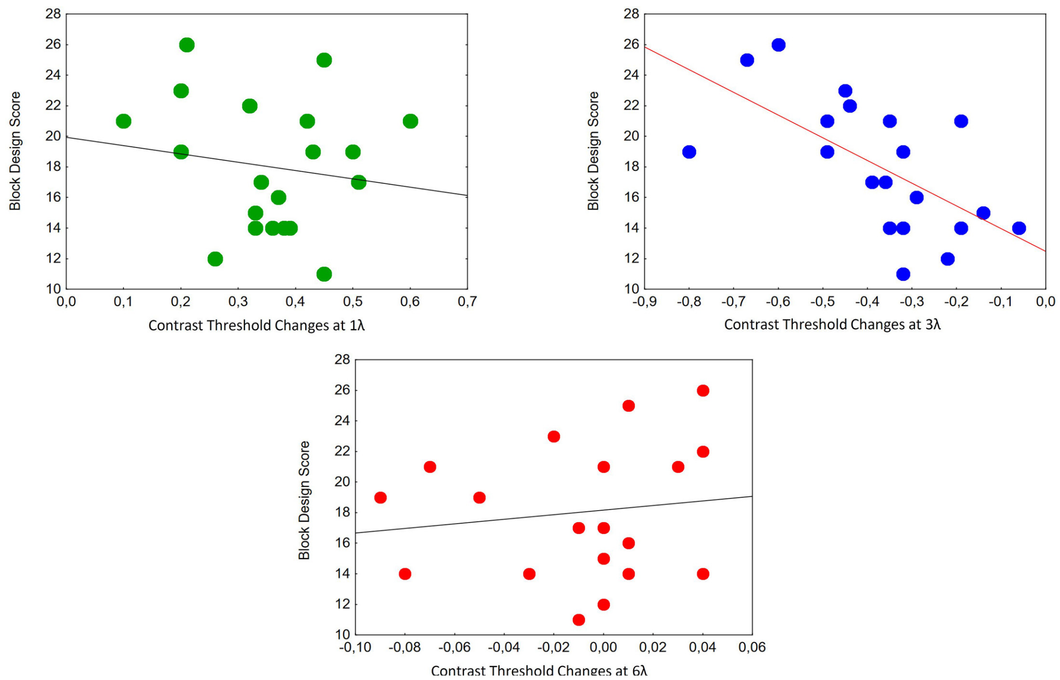

FIGURE 4 | Correlations between contrast threshold changes and Block Design Scores at different target-mask distances in the perception task in individuals with ASC exhibiting a Block Design peak performance ($n = 20$). A significant relationship was found at 3λ (partial $r = -0.65$, $p < 0.01$).

and neural network approach to map feedforward, horizontal, and recurrent feedback processing in ASC. They found abnormal object boundary detection as early as 120 ms after stimulus presentation, which may be a marker of dysfunctional lateral connections in early visual areas. Interestingly, ASC individuals were characterized by an enhanced subsequent occipital activity (225 ms), whereas recurrent feedback processing from extrastriate areas (260 ms) was spared (Vandenbroucke et al., 2008).

We also found weak inhibition at small target-mask distances (1λ) in the ASC Peak group. This is consistent with a previous functional magnetic resonance imaging study demonstrating a correlation between weaker surround suppression in the V1 and autistic traits in the general population (Flevaris and Murray, 2014), although brain imaging studies using the lateral masking paradigm have not been performed. Therefore, the interpretation of our behavioral results at the neuronal level is indirect. However, Dickinson et al. (2018) showed that greater severity of autistic symptoms was associated with increased short-range lateral inhibition. The authors concluded that lateral connections were not generally dysfunctional in ASC, and subtle alterations and individual variations might explain the heterogeneity of visual perceptual phenotype (Bertone et al., 2005; Dickinson et al., 2018). These divergent results may stem from different methods and from the heterogeneity of ASC.

Classic models suggest that the facilitatory effect of collinear masks is due to the spreading of excitatory signals from the mask-responsive to the target-responsive cells *via* lateral connections in the V1 (Livingstone and Hubel, 1984; Gilbert and Wiesel, 1989; Polat and Sagi, 1993). Feedback from higher cortical areas may strengthen the attentional modulation of collinear masks and targets (Gilbert et al., 2000; Freeman et al., 2003), although lateral facilitation seems to be too fast for such feedback effects (Yu et al., 2002). Specifically, lateral facilitation by collinear masks was demonstrated at a stimulus duration as brief as 8 ms, a timing too short for cortical feedback (Yu et al., 2002). According to the models of temporal dynamics, there are two possible components of facilitation. The first is a fast and short-acting component of facilitation that involves a single spatially-elongated perceptual channel defining the classic receptive field without long-range connections (Georgeson and Georgeson, 1987). The second is a delayed and long-acting component that is based on long-range connections between collinear flanker masks and target (Polat and Sagi, 2006). Huang and Hess (2008) showed that these models are not sufficient and that the dynamics of perceptual facilitation are both fast and sustained. The authors proposed a two-component model of facilitation consisting of a rapid signal across large retinal distances based on feedback from higher centers and a sustained, lower-level response involving the temporal integration of locally responsive mechanisms (Huang and Hess, 2008). Therefore, the main point of the Huang and Hess (2008) model, which is based on a series of psychophysical studies, is that facilitation is neither delayed and long-lasting, not fast and short-lived. Instead, facilitation is fast and sustained. Contrary to the classic view, the fast signal is based on feedback, whereas the sustained response is mediated by low-level mechanisms. In sharp contrast to lateral facilitation, masks can inhibit target detection if the target-mask distance is small ($<2\lambda$). This lateral inhibition is thought to be related to short-range inhibitory connections (Blakemore et al., 1970; Polat and Sagi, 1993; Shushruth et al., 2013). At the behavioral level, our results indicate that both excitatory and inhibitory lateral connections are altered in ASC Peak, characterized by enhanced excitation at intermediate target-mask distances (3λ) and reduced inhibition at small target-mask distances (1λ). This raises the possibility that autism-related developmental alterations in visual cortical circuits are not confined to a single mechanism, and that these can be detected especially in individuals with ASC who display exceptional visuoconstructional abilities.

We also identified a robust dissociation between perception and imagery: individuals with ASC, irrespective their visuoconstructional abilities, displayed a negligible imagery effect. It is possible that they failed to imagine the masks or the imagined masks failed to modulate the target. However, given that there were normal (ASC Non-Peak) or enhanced (ASC Peak) lateral interactions in the perceptual task, it is not likely that successfully imagined masks failed to act on the target. Overall, the dissociation between perception and imagery indicates enhanced early bottom-up perception and dampened top-down control in the ASC Peak group, whereas in the ASC Non-Peak group, weak top-down control was accompanied by unaltered perception.

Our results provide a plausible explanation for an important controversy in the literature. While Kéïta et al. (2011) reported increased lateral facilitation in individuals with ASC relative to controls, Jachim et al. (2015) found the opposite phenomenon, that is, weak facilitation in ASC. Notably, the sample of Jachim et al. (2015) included individuals with Asperger's syndrome, which was not the case in the Kéïta et al.'s (2011) study. Differences in the experimental design could also contribute to the discrepancy of results. Kéïta et al. (2011) used long exposure time and added gray scale noise to the stimulus display, raising the possibility that noise differently interfered with perceptual processing in ASC and healthy controls. In our study, the stimulus exposure time was short, and no noise was applied, excluding the possibility that these parameters accounted for the difference in previous studies. Moreover, we controlled individual variations in cognitive developmental patterns (ASC Peak vs. ASC Non-Peak). However, it cannot be excluded that individuals with Asperger's syndrome exhibit a distinct pattern of lateral masking performance. Furthermore, it is important to take into account that our participants were male, and the results may not be generalized to female individuals.

The finding that heightened Block Design performance was associated with poor imagery seems to be counterintuitive, because in a previous study Block Design performance was related to a more efficient imagery and manipulation of mental representations (Soulières et al., 2011). The authors conducted mental imagery experiments in 23 individuals with ASC (11 with Block Design peak) and 14 matched neurotypical controls. In the first experiment, participants were asked to imagine a letter inside a circle, whereas the second experiment included mental rotation tasks with two- and three-dimensional shapes, hands and letters. Individuals with ASC, especially those with Block Design peak, were more accurate in the imagery tasks relative to the controls. These results can be explained in the framework of a global advantage in perceptual processing (enhanced perceptual functioning model) or by an eminence in veridical mapping, which refers to the ability to detect isomorphisms among objects (Soulières et al., 2011). However, mental imagery abilities depended on the task type: the performance was more pronounced when the task included the mental rotation of three-dimensional objects rather than more simple two-dimensional shapes, hands, or letters (Soulières et al., 2011). Therefore, it is possible that imagery is even less effective in the case of low-level luminance contrast gratings, as shown in the present study. At the neuronal level, there is evidence that people with ASC show higher activation in a widespread parietal and occipital network during the Block Design task relative to non-autistic controls, but this enhanced neuronal network does not include the V1, which is critical in the lateral masking task (Polat and Sagi, 1993; Kana et al., 2013).

Decreased performances on the mental imagery task may be related to the impaired top-down control of information processing in ASC. At the neuronal level, it may be due to deficits in visual cortical areas, control areas (prefrontal cortex), or the connectivity between the sensory and control regions (Frith, 2003; Loth et al., 2010; Cook et al., 2012; Van Der Cruys et al., 2018). Our study could not explore these possibilities at the neural level, and it is not clear whether individuals with ASC failed to imagine the masks or the successfully imagined mask failed to exert an effect on the target. However, previous studies indicated that people with ASC exhibit normal (Kana et al., 2006) or even enhanced visual imagery (Soulières et al., 2011) using more complex stimuli. It has also been shown that non-visual cognitive control might play a compensatory role in imagery in ASC. When participants were asked to memorize a map of a fictitious island, verbal IQ and working memory were positively associated with image scanning performance in ASC, but not in healthy controls (Maras et al., 2014). In the present study, verbal compensation was not possible because of the simplicity of stimuli.

In the framework of the Bayesian decision theory, Pellicano and Burr (2012) suggested that atypical perceptual experiences in ASC can be explained by a deficient interaction between incoming sensory information and a prior knowledge of the world. Specifically, attenuated top-down influences (Bayesian "hypo-priors") may induce a hyper-realistic perception, which is weakly influenced by past experiences. In our paradigm, prior experiences did not influence the detection of the target stimulus when participants were requested to retrieve and to imagine the previously presented masks. This suggests that the diminished effect of prior experiences can be revealed at the early stage of visual processing in ASC.

The general loss of imagery in ASC may stem from nonspecific factors (e.g., a misunderstanding of the instructions or a lack of motivation), and this is a main limitation of the study. However, individuals with ASC excellently performed on challenging neuropsychological and psychophysical tests in this study, even displaying better performances than healthy control subjects in some domains. Generally, as discussed above, individuals with ASC do not show impaired visual mental imagery (Kana et al., 2006; Soulières et al., 2011; Maras et al., 2014). The imagery condition was matched to the perception condition in task structure and general difficulty, and we made sure during the practice block that individuals with ASC understood the task correctly. Moreover, in our previous study, individuals with schizotypal personality disorder, who often find testing situations very challenging due to their decreased motivation, distractibility, and suspiciousness, exhibited enhanced (more effective) mental imagery relative to control participants, which is against the possibility that the imagery task is more difficult to understand or motivationally more demanding than the perceptual task (Maróthi and Kéri, 2018). Finally, a rating scale for fatigue and motivation did not indicate significant differences between individuals with ASC and healthy control participants.

In conclusion, our results provide psychophysical evidence for a unique pattern of lateral interactions in the V1 of individuals with ASC Peak: a decreased inhibition at short distance (1λ of target-mask distance) and an enhanced facilitation at intermediate distances (3λ of target-mask distance). The decreased horizontal inhibition in early-stage vision may be relevant to several assumptions of the enhanced perceptual theory and the weak central coherence hypothesis of autism (Happé and Frith, 2006; Mottron et al., 2006). Because of the decreased inhibition of adjacent stimuli (masks) on a central target, ASC Peak individuals may exhibit a detail-focused processing rather than a holistic perception of larger images (Happé and Frith, 2006). Specifically, decreased lateral inhibition exerted on a small spatial region (i.e., the target Gabor patch in the lateral masking task) may lead to the pop-out and enhanced perceptual awareness of this spot. From another point of view, low inhibition and high facilitation in the lateral connections of the V1 may lead to a better detection of elementary visual features and simple contours (Mottron et al., 2006; Loffler, 2008). The biological bases of these findings remain to be explored: inhibition-excitation ratio in the V1 is a possible target for future investigations (Robertson et al., 2016).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Medical Research Council. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SK, KC, and RM designed the study. RM coordinated data collection and measurements. RM and SK analyzed the data. RM, KC, and SK wrote the first draft of the article, which was reviewed, edited, and approved by both authors.

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Contact Heat Evoked Potentials Are Responsive to Peripheral Sensitization: Requisite Stimulation Parameters

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The sensitizing effect of capsaicin has been previously characterized using laser and contact heat evoked potentials (LEPs and CHEPs) by stimulating in the primary area of hyperalgesia. Interestingly, only CHEPs reveal changes consistent with notion of peripheral sensitization (i.e., reduced latencies). The aim of this study was to investigate contact heat stimulation parameters necessary to detect peripheral sensitization related to the topical application of capsaicin, and therefore significantly improve the current method of measuring peripheral sensitization via CHEPs. Rapid contact heat stimulation (70°C/s) was applied from three different baseline temperatures (35, 38.5, and 42°C) to a 52°C peak temperature, before and after the topical application of capsaicin on the hand dorsum. Increased pain ratings in the primary area of hyperalgesia were accompanied by reduced N2 latency. Changes in N2 latency were, however, only significant following stimulation from 35 and 38.5°C baseline temperatures. These findings suggest that earlier recruitment of capsaicin-sensitized afferents occurs between 35 and 42°C, as stimulations from 42°C baseline were unchanged by capsaicin. This is in line with reduced thresholds of type II A-delta mechanoheat (AMH) nociceptors following sensitization. Conventional CHEP stimulation, with a baseline temperature below 42°C, is well suited to objectively detect evidence of peripheral sensitization.

Keywords: capsaicin, contact heat evoked potentials, type II A mechanoheat nociceptors, EEG, hyperalgesia

INTRODUCTION

Approximately one in five individuals live with chronic pain (Schopflocher et al., 2011; Kuehn, 2018), with a combined economic impact greater than cancer, HIV, and heart disease combined (Phillips, 2009). The sensitization of nociceptive neurons in the periphery is often a key first step in the development of persistent and chronic pain (Latremoliere and Woolf, 2009). The study of

Abbreviations: AMH, A-delta mechanoheat nociceptors; CHEPs, contact heat evoked potentials; LEPs, laser evoked heat potentials; TRPV-1, transient receptor potential cation channel subfamily V member 1.

chronic pain, and the development of sensitization, has long relied on the experimental induction of pain via controlled noxious stimuli, such as capsaicin (Basbaum et al., 2009; Latremoliere and Woolf, 2009; Woolf, 2011). The topical application of capsaicin results in a predictable area of primary hyperalgesia (LaMotte et al., 1991; Kilo et al., 1994), a key indicator of peripheral sensitization. The sensitizing effect of capsaicin is readily detected in humans as reduced heat pain thresholds and increased sensitivity to mechanical stimuli. Based on its robust, reversible, and minimally-invasive nature, capsaicin represents a widely popular, translational pain model to investigate analgesic drug properties and neuromodulatory effects (Kazarinov et al., 1977; Poyhia and Vainio, 2006; Jutzeler et al., 2015; Larsen et al., 2018; Vollert et al., 2018).

The underlying mechanisms of capsaicin induced primary hyperalgesia are attributable to sensitization of transient receptor potential cation channel subfamily V member 1 (TRPV-1) (Rosenbaum and Simon, 2007). Specific fiber types sensitized by capsaicin include type II AMH nociceptors (Ringkamp et al., 2001; Dubin and Patapoutian, 2010). These afferents are responsible for conveying "first pain," typically recruited following thermal stimulation at or above 42°C (Treede et al., 1995, 1998; Harkins et al., 2000; Arendt-Nielsen and Chen, 2003), and commonly investigated in humans using contact heat and laser evoked potentials (CHEPs and LEPs) (Harkins et al., 2000; Chen et al., 2001; Iannetti et al., 2006).

In line with behavioral signs of sensitization, CHEPs are modulated following application of capsaicin and stimulation in the primary area of hyperalgesia. This is evidenced as increased pain ratings and reductions in N2 waveform latency (Madsen et al., 2012; Jutzeler et al., 2015). However, an understanding of latency reductions and neural processes involved remains unknown.

One possibility for N2 latency reductions in response to capsaicin is that type II AMH afferents are temporally recruited earlier in the periphery during contact heat stimulation. Conventionally, contact heat stimulation is delivered from a low (e.g., 35°C) baseline to a peak temperature (e.g., 52°C) at a fixed, nominal rate (e.g., 70°C/s) (Kramer et al., 2012a,b, 2013, 2016; Haefeli et al., 2013, 2014b). This means that stimulation passes through lower temperatures before activating type II AMH nociceptors (at $\geq\sim$42°C) (Baumgartner et al., 2005). After the topical application of capsaicin, type II AMH nociceptor threshold is reduced (e.g., to 38–40°C), which results in earlier onset CHEPs (i.e., reduced latency).

To test this theory, we examined CHEPs in the primary area of hyperalgesia using three different baseline temperatures (i.e., 35, 38.5, and 42°C). Elevated baseline temperatures were intended to decrease recruitment of afferents by contact heat stimulation below the normal threshold of type II AMH nociceptors ($\sim$42–46°C) (Treede et al., 1995, 1998; Harkins et al., 2000; Arendt-Nielsen and Chen, 2003). We hypothesized that applying baseline temperatures of 38.5 and 42°C would attenuate reductions in N2 latency compared to 35°C baseline stimulation. Our findings will improve the understanding of neuromodulatory influences of CHEPs N2 latencies in the assessment of peripheral sensitization in humans.

MATERIALS AND METHODS

Subjects

Thirteen healthy subjects without a history of chronic pain and neurological disease participated in the study. Exclusion criteria comprised pregnancy, intake of any medication (except birth control), and any obvious neurological condition. The experimental protocol conformed to the standards set by the Declaration of Helsinki and was approved by the local ethical committee. All subjects gave written informed consent.

Experimental Design

In the current study, all subjects participated in two CHEP recording sessions. Experimental sessions were separated by at least 48 hours, to a maximum of 7 days. In the second recording session, subjects underwent 30 min of topical capsaicin sensitization prior to contact heat stimulation (**Figure 1**).

Contact Heat Stimulation

A contact heat stimulator (PATHWAY Pain and Sensory Evaluation System; Medoc, Ramat Yishai, Israel) was used to deliver noxious heat stimuli. The thermode (27 mm diameter with a stimulating surface of 572.3 mm^2) is composed of a heating thermofoil covered with a thermo conductive plastic. The thermofoil allows a heating rate of 70°C/s and is actively cooled by a peltier element (40°C/s). Contact heat stimuli were applied in an area [approximately 16 cm^2 (1600 mm^2)] within the boundaries of the C6 dermatome, on the dorsum surface, at the base of the thumb from three baseline temperatures (35, 38.5, and 42°C) in random order. These were selected to represent starting points below (35 and 38.5°C) and at/above type II AMH nociceptor thresholds ($\sim$42°C). The order of stimulation was randomized between subjects and maintained across the first and second experimental session. Irrespective of the baseline temperature, the target peak stimulation intensity was set to 52°C. The different baseline temperature conditions are displayed in **Figure 1**. For each condition, 10 stimulations (Kramer et al., 2013, 2016) were applied with an 8–12 s inter-pulse interval (Jutzeler et al., 2016; Rosner et al., 2018). A low number of stimulations was used to avoid peripheral sensitization caused by repetitive cutaneous stimulation. A total of 30 stimulations were performed on each testing day. After each contact heat stimuli, the thermode was repositioned within a 16 cm^2 (1600 mm^2) boundary (i.e., lifted from the skin and placed at a different location within the outlined area) to reduce receptor fatigue (Greffrath et al., 2007). As a result, no two consecutive stimulations were performed in exactly the same area. The same procedure was performed in the capsaicin as in the no-capsaicin condition. Subjects rated the perceived intensity using a numeric rating scale ranging from 0 to 10 after each stimulus (0-no pain, 10-worst pain imaginable). Subjects were asked to keep their eyes open during contact heat stimuli and blink, if necessary, to an acoustic cue presented 4 s after stimulation.

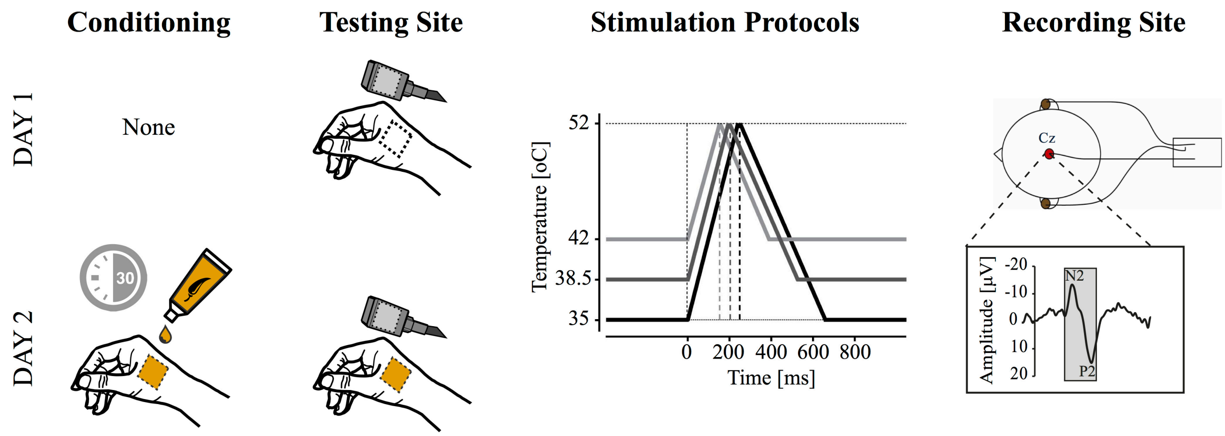

FIGURE 1 | Study design. Contact heat evoked potentials (CHEPs) were acquired on separate testing days (i.e., with and without capsaicin). Capsaicin was applied topically for 30 min prior to CHEPs acquisition on day two. CHEP stimulation was applied from three baseline temperatures: (1) 35°C, (2) 38.5°C, and (3) 42°C to a peak temperature of 52°C. These resulted in stimulus durations of 243, 193, and 143 ms (i.e., onset to peak), respectively. The order of baseline temperature was randomized, but maintained between experimental sessions. All stimuli were delivered to a 52°C peak temperature. A vertex recording electrode (Cz, referenced to linked ears) was used to acquire the most prominent CHEP (i.e., N2P2).

Capsaicin Application

Capsaicin was applied preceding contact heat stimulation in the second CHEP recording session. One ml of 0.075% capsaicin cream (Hänseler, Herisau, Switzerland) was applied to a 16 cm^2 area within the boundaries of the C6 dermatome. Similar concentrations of capsaicin have been applied previously to induce experimental pain (Srbely et al., 2010; Andresen et al., 2011; Jutzeler et al., 2015; Linde and Srbely, 2019). The 16 cm^2 (1600 mm^2) area was limited by tape. During capsaicin sensitization, subjects were asked to rate their pain on a numeric rating scale from 0 to 10 every 5 min. After 30 min of capsaicin sensitization, the remaining cream was removed.

CHEP Recording

For the electroencephalography scalp recording sites were prepared with alcohol and Nuprep (D.O. Weaver and Company, Aurora, CO, United States). Gold cup electrodes were positioned on Cz and referenced to linked earlobes (Cz-A1-A2) to record N2 and P2 waveforms. A wet ground strap was attached to the subjects' forearm. We used a reduced electrode set up as numerous previous studies have reliably produced N2 and P2 waveforms from the Cz electrode referenced to linked earlobes (Treede et al., 1988; Bromm and Chen, 1995; Kakigi et al., 2004; Wydenkeller et al., 2008; Kramer et al., 2012a,b; Albu et al., 2013; Jutzeler et al., 2015, 2016; Rosner et al., 2018). CHEPs were sampled at 2000 Hz using a preamplifier (20000×, bandpass filter 0.25–300 Hz; ALEA Solutions, Zurich, Switzerland). Data were recorded in a Labview based program (V1.43 CHEP; ALEA Solutions, Zurich, Switzerland) using a time-frame of 100 ms pre-trigger and 1000 ms post-trigger. Data were bandpass filtered offline with a 0.5–30 Hz filter.

Data Analysis

EEG Epochs from −100 pre-trigger to +1000 ms post-trigger were visually analyzed by a blinded and experienced examiner (JH), without knowledge of stimulation conditions or the baseline temperatures. A minimum of nine artifact (e.g., blink) free trials was included for N2 and P2 waveform averaging within each condition for each participant. The average number of trials included in CHEPs waveform averaging was 9.81 ± 0.40 (Mean ± SD). Two separate examiners (CJ and JK) confirmed N2 and P2 waveforms. Disagreement was discussed between examiners until consensus was reached. CHEPs parameters (N2 latency, N2 amplitude, P2 latency, P2 amplitude, and N2P2 amplitude) were calculated from averaged waveform data.

All statistical analyses were performed in R (Version 3.5.3, MacOs Mojave). The skewed distribution of CHEP parameters was corrected by log transformation. A linear mixed effects model with repeated measures was first applied to examine the relationship between time and perceived intensity of capsaicin application over 30 min. A second linear mixed effects model examined the main effects of baseline temperature (35, 38.5, and 42°C) and capsaicin application on log-transformed CHEP outcomes. Interactions between baseline temperature and capsaicin were examined to delineate whether baseline temperature had a differential effect on CHEPs outcomes. The model was adjusted for the stimulation order. *Post hoc* pairwise comparisons were Bonferroni corrected. Statistical significance was set at $\alpha = 0.05$. All of the data used in our analysis, extracted from CHEP waveforms, is shown in **Supplementary Table S1**.

RESULTS

One subject could not tolerate any contact heat stimulation during application with capsaicin and was excluded from analysis. The average age of the remaining 12 subjects (10 males) was 31.5 ± 7.7 years (± SD).

Capsaicin Sensitization Period

In agreement with the known effects of topically applied 0.075% capsaicin cream, there was a significant main effect of time on pain intensity rating (β = 0.155, CI [95%]: 0.13 – 0.18, $p < 0.001$) (**Figure 2**).

Main Effect of Capsaicin Sensitization

The grand-average CHEPs for all baseline temperature condition with and without capsaicin sensitization are illustrated in **Figure 3A**. A representative example is illustrated in **Figure 4**.

Overall, pain ratings to the contact heat stimulation were significantly higher after the capsaicin sensitization (β = 0.34, CI [95%]: 0.17 – 0.51, $p < 0.001$) (**Figure 3B**). This is consistent with the known effect of capsaicin to induce hyperalgesia to heat in the primary area of application. CHEP amplitudes (i.e., N2P2, N2, and P2) and P2 latency were unaffected by capsaicin [N2P2 amplitude: β = 0.07, CI [95%]: −0.08 – 0.22, p = 0.365 (**Figure 3C**); N2 amplitude: β = 0.10, CI [95%]: −0.09 – 0.29, p = 0.296; P2 amplitude: β = 0.02, CI [95%]: −0.16 – 0.21, p = 0.823; P2 latency β = −0.05, CI [95%]: −0.10 – 0.00, p = 0.082]. Overall, N2 latency was significantly reduced after capsaicin sensitization (β = −0.17, CI [95%]: −0.22 – −0.12, $p < 0.001$) (**Figure 3D**).

Interaction of Baseline Temperature Condition and Capsaicin Application

There was a significant interaction effect between baseline temperature condition and capsaicin sensitization for N2 latency (42°C: β = 0.14, CI [95%]: 0.07 – 0.21, $p < 0.001$). This suggests that the reduction in N2 latency depended on the baseline temperature. At 35°C and 38.5°C baseline temperatures, N2 latency was significantly shorter after capsaicin sensitization (35°C: β = −0.17, CI [95%]: −0.24 – −0.10, $p < 0.001$; 38.5°C: β = −0.07, CI [95%]: −0.11 – −0.02, p = 0.011). Only one subject did not demonstrate a decreased N2 latency following the application of capsaicin and stimulation from a 35°C baseline temperature. From a 38.5°C baseline temperature, only three subjects demonstrated a nominal increase in N2 latency. N2 latencies were comparable before and after capsaicin for 42°C baseline condition (β = −0.03, CI [95%]: −0.06 – 0.01, p = 0.166; **Figure 3D**). There were no interaction effects (baseline temperature condition and capsaicin) for N2P2 amplitude or P2 latency. Model summaries from the statistical analysis are shown in **Supplementary Tables S2**, **S3**.

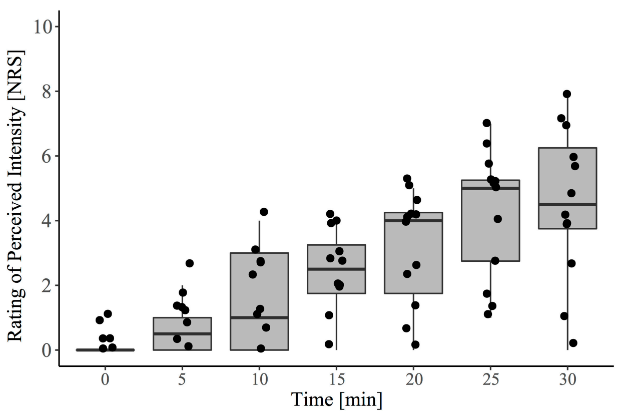

FIGURE 2 | Pain ratings to capsaicin exposure over the 30-minute conditioning period (i.e., pre-contact heat stimulation). During this time, participants sat quietly and were instructed to rate spontaneously perceived intensity (0–10) to the area of capsaicin application every 5 min. The baseline (time 0) recording represents the reported sensation immediately after capsaicin was applied to the entire area. Contact heat stimulation and the acquisition of evoked potentials were performed at 30 min, following cream removal.

Addendum to Results

We acquired CHEPs from an additional six participants (3 males, age 25 ± 3.5 years) to confirm that the number of stimulations used in CHEPs acquisition was not a limitation to our findings. Six participants completed study procedures as outlined above; the only methodological difference was that participants received 20 contact heat stimuli per baseline temperature as opposed to 10 stimuli. EEG data was recorded from 32 active electrodes via international 10–20 positioning (REF) (Brain Vision LLC, Morrisville, NC, United States). CHEPs waveforms were calculated from the Cz vertex position, referenced to linked earlobes. N2 latencies were calculated from averaged waveform data using the first 10 stimuli and all 20 stimuli of EEG epochs 100 ms pre-stimulus to 1000 ms post-stimulus. All CHEPs waveforms were visually inspected for artifacts (i.e., blink). The average number of trials used in CHEPs waveform averaging was 19.77 ± 0.76 for 20 stimuli and 9.88 ± 0.34 for 10 stimuli, respectively. N2 latencies were compared between 10 and 20 stimuli methods of calculation, using two-sample t-tests. We observed no significant differences between N2 latencies calculated from 10 stimuli vs. 20 stimuli for all baseline temperature stimulation protocols (35°C: 20 stimuli – 361 ms, CI [95%]: 338–381; 10 stimuli – 366 ms, CI [95%]: 346–385, p = 0.72; 38.5°C: 20 stimuli – 302 ms, CI [95%]: 289–316; 10 stimuli – 291 ms, CI [95%]: 283–298, p = 0.20; 42°C: 20 stimuli – 268 ms, CI [95%]: 261–276; 10 stimuli – 265 ms, CI [95%]: 255–276, p = 0.71) (**Supplementary Table S4**).

We also examined the influence of capsaicin on N2 latency between baseline temperatures for this additional N = 6 dataset. Similar to our original findings, we observed a main effect of capsaicin sensitization on N2 latency (β = −0.15, CI [95%]: −0.23 – −0.07, p = 0.001) as well as an interaction effect of capsaicin and baseline temperature (42°C: β = 0.16, CI [95%]: 0.05 – 0.27, p = 0.01). This interaction effect suggests that the reduction in N2 latency depended on the baseline temperature. At the 35°C baseline temperature, N2 latency was significantly reduced after capsaicin sensitization (β = −0.15, CI [95%]: −0.24 – −0.05, p = 0.014). At 38.5 and 42°C baseline temperatures, there was no significant effect of capsaicin on N2 latency (38.5°C: β = −0.04, CI [95%]: −0.12 – 0.04, p = 0.364; 42°C: β = 0.00, CI [95%]: −0.05 – 0.06, p = 0.892) (**Supplementary Table S5**). Only 1 of 6 participants did not demonstrate a decreased N2 latency following the application of capsaicin and stimulation for both 35 and 38.5°C baseline

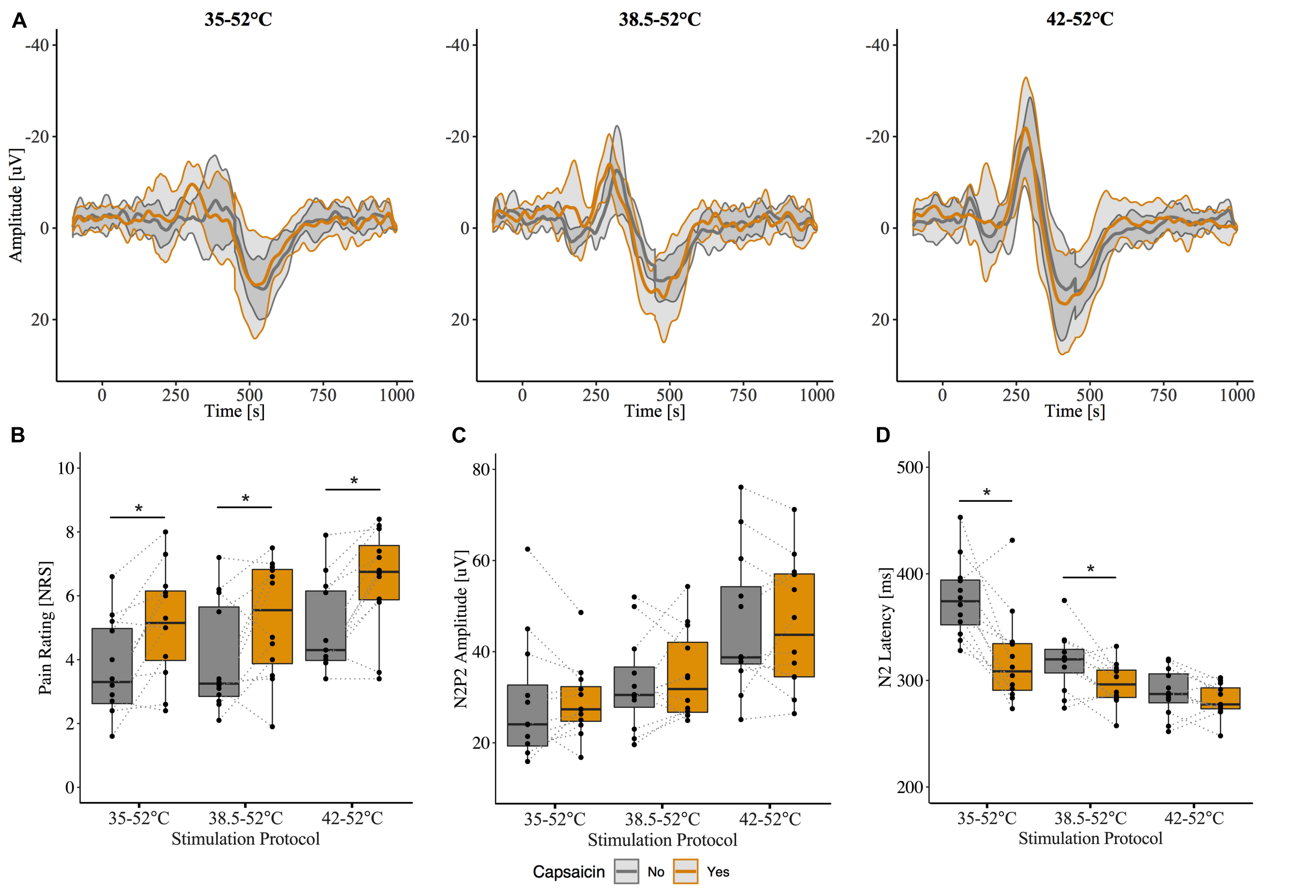

FIGURE 3 | Effect of capsaicin on contact heat evoked potentials (CHEPs). **(A)** Grand-average N2P2 waveforms from all subjects (n = 12). Shaded area represents between subject standard deviation. **(B)** Pain ratings, **(C)** N2P2 amplitude, **(D)** N2 latency before and after capsaicin. Pain ratings were significantly increased following capsaicin application for all baseline temperatures. N2 latency was significantly affected by capsaicin and only when stimulation was performed from 35 and 38.5°C baseline temperatures. * Denotes a significant difference between capsaicin "Yes" and "No" sessions for respective baseline temperatures, $p < 0.05$.

temperatures, however, the effect of capsaicin did not reach statistical significance for the 38.5°C baseline temperature. Similar to our original findings, N2 latencies were comparable before and after capsaicin application for the 42°C baseline temperature (**Figure 5**).

DISCUSSION

As in previous CHEP studies applying conventional baseline temperature stimulation (Madsen et al., 2012; Jutzeler et al., 2015), N2 latency was reduced and pain rating increased following stimulation in the primary area of hyperalgesia. The effect of sensitization on N2 latency was significant when stimulation at 35 and 38.5°C baselines. Increasing the baseline temperature to 42°C attenuated latency reductions, to the point that N2 latency was not significantly different following sensitization. These findings were replicated in our additional dataset, with significant reductions in N2 latency observed at 35°C baseline, non-significant reductions in N2 latency at 38.5°C in five of six additional participants, and comparable N2 latencies following capsaicin application for 42°C baseline. Together, these findings from both our original and additional dataset suggest that recruitment of capsaicin-sensitized afferents occurs below 42°C.

N2 latencies obtained during the control session from 35°C and 42°C baseline temperature conditions were in line with previously reported normative values for the C6 dermatome (Jutzeler et al., 2016). The N2 latencies following capsaicin application in the 35°C baseline condition [319.8 ± 43.9 ms (mean ± SD)] were significantly earlier than the control condition (376.8 ± 45.1 ms) and were also earlier than previously reported normal values for N2 latencies (384.1 ± 31.9 ms) (Jutzeler et al., 2016). This trend was replicated in our additional validation dataset, with pre-capsaicin N2 latencies (387.0 ± 8.5 ms) in line with previously reported normal values (384.1 ± 31.9 ms) and post capsaicin N2 latencies (334.2 ± 42.8 ms) shifting to precede previously reported normal values (Jutzeler et al., 2016). Together, these findings suggest the effect of capsaicin on N2 latency, acquired via 35°C baseline, was both statistically significant and clinically relevant,

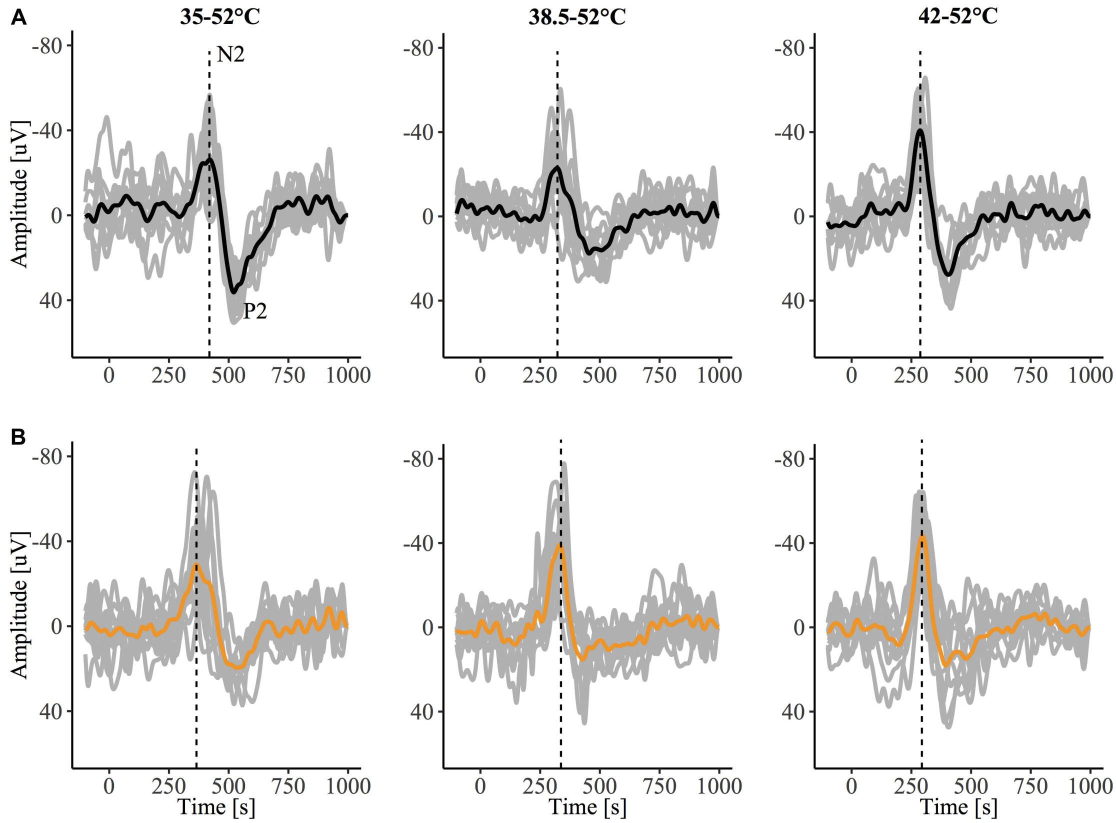

FIGURE 4 | Contact heat evoked potentials (CHEPs) from a representative subject before **(A)** and after **(B)** capsaicin sensitization, recorded in response to stimulation from a 35, 38.5, and 42°C baseline. The dotted vertical line denotes N2 latency, observed to be earlier in the 35°C baseline condition following capsaicin sensitization in this representative tracing.

as sensitized N2 latencies occurred earlier than previously reported normal values.

Our findings also clearly demonstrate that reduced N2 latency is not related to thermal hyperalgesia *per se*. This was evidenced by the fact that pain ratings significantly increased in the primary area of hyperalgesia for all baseline temperature stimulations, even in the absence of reduced N2 latency (i.e., 42°C baseline temperature CHEP stimulation). This temperature dependent dichotomy of the effect of capsaicin on pain ratings and N2 latencies in response to contact heat may suggest separate mechanisms of peripheral sensitization. Previous studies in both humans and animals have suggested primary hyperalgesia to be mediated by the sensitization of C-fiber nociceptors, while secondary hyperalgesia is mediated by sensitized A-fiber nociceptors (Culp et al., 1989; Hsieh et al., 2015). Given our stimulation site was within the area of primary hyperalgesia and given the neural pathway of CHEPs activation via type II AMH nociceptors (Chen et al., 2001; Iannetti et al., 2006; Truini et al., 2007), a possible explaination for our findings may be that pain ratings were influenced by C-fiber sensitzation, while reductions in N2 latencies were mediated by the sensitiztion of type II AMH nociceptors. Future studies should explore this avenue further through the use of nerve block or compression ischemia testing during CHEPs acquisition with capsaicin.

There is little debate that the neural signature of contact heat stimulation (i.e., vertex N2P2 waveform) arise from activation of type II AMH nociceptors (Chen et al., 2001; Iannetti et al., 2006; Truini et al., 2007). It logically follows that sensitizing type II AMH nociceptors with capsaicin should lead to profound changes in CHEPs. Our findings replicate those of previous CHEP studies using similar stimulation parameters (35 to 52°C at 70°C/s) (Madsen et al., 2012; Jutzeler et al., 2015), in that N2 latency was reduced and pain rating increased in the primary area of hyperalgesia. The most pragmatic explanation for a reduction in N2 latency is that capsaicin modulates type II AMH nociceptors, lowering their activation threshold to thermal stimulation. From lower baseline temperatures, threshold is reached faster, temporally recruiting the same or similar population of thinly myelinated afferents earlier in the heat stimulus.

Consistent with the notion of earlier recruitment, stimulation from more conventional baseline temperatures (e.g., 35°C) was a requisite parameter to detect significant reductions in N2 latency. Higher temperatures failed to reveal the sensitizing effect of capsaicin. From a 42°C baseline, recruitment of type II AMH nociceptors may already occur as fast as is physiologically possible. Recruitment occurs at or above the normal threshold for activation of type II AMH nociceptors, creating a "floor

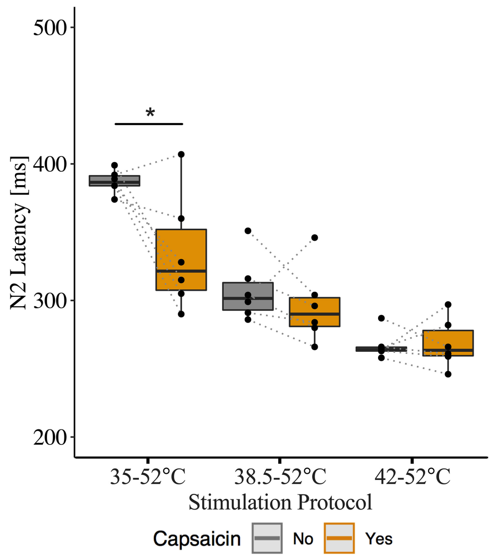

FIGURE 5 | Effect of capsaicin on contact heat evoked potentials (CHEP) N2 latency with stimulations delivered at 35, 38.5, and 42°C baselines. Data displayed from additional six participants, that underwent 20 stimulations per condition as opposed to 10 stimulations. * Denotes a significant difference between capsaicin "Yes" and "No" sessions for respective baseline temperatures, $p < 0.05$.

effect" that prevents the measurement of peripheral sensitization. Overall, these observations suggest that stimulation between 35 and 42°C is key to detecting peripherally sensitized type II AMH afferents, which coincides with behavioral evidence of sensitization below 40°C (Schaldemose et al., 2015).

Contact heat stimulation is now widely regarded as sufficient for the acquisition of nociceptive evoked potentials. CHEP stimulation slowly activates nociceptors, sequentially, from a starting baseline temperature below the recruitment threshold of type II AMH afferents (e.g., 35°C). As is evident in **Figure 4**, even a low number of stimulations (10) yield a larger and reliable vertex waveform, particularly at higher baseline temperatures. This is in line with previous CHEPs studies (Kramer et al., 2013, 2016), and was further demonstrated in our own comparison between N2 latencies calculated from 10 stimuli to 20 stimuli, respectively. However, compared to other forms of noxious stimulation (e.g., laser), evoked potentials arising from contact heat stimulation are less synchronized and subject to greater temporal dispersion and higher latency jitter (variability in latency among averaged trials) (Granovsky et al., 2008). Nevertheless, contact heat stimulation may present an opportunity to specifically and objectively assess the role of peripheral sensitization (i.e., lowering of type II AMH nociceptor thresholds below 42°C). Future studies directly comparing laser and CHEPs are needed to comprehensively evaluate sensitivity and optimal stimulation parameters to detect primary hyperalgesia.

Our control observations (i.e., changing baseline temperature in the absence of capsaicin) demonstrate an obvious advantage of increasing the baseline temperature to acquire CHEPs N2P2 amplitudes. This confirms our previous findings (Kramer et al., 2012a, 2013; Haefeli et al., 2014a). The impact of increasing the baseline temperature on contact heat evoked potentials is chiefly a function of increasing correspondence between the theoretical and acute peak temperature experienced at the nociceptor. From a 35°C baseline, at 70°C/s, only a fraction of the nominal peak temperature is reached at the level of the nociceptors (Baumgartner et al., 2005). This represents a well-known technical challenge, which is due to the temperature of the skin lagging behind the temperature of the thermode. As a result, the thermode returns to baseline (i.e., actively cooling) before the skin (or the nociceptor) ever reaches the desired peak temperature. Shifting the starting point of contact heat stimulation to higher temperatures simply means that higher peak temperatures can be physiologically achieved. This, in turn, recruits a larger number of afferents, yielding higher pain ratings and increased CHEP amplitudes. Other factors, like improving synchronization of the afferent volley by shortening the stimulus duration, may also play a role in generating larger amplitude evoked potentials (Iannetti et al., 2004).

An alternative explanation for our results is that peripheral sensitization shifted recruitment to larger and faster conducting type II AMH afferents. From a 35°C baseline temperature, a reduction in CHEP latency occurs because control stimulation recruits slower conducting afferents. Higher baseline temperatures fail to convey a change in latency shift, chiefly because the fastest conducting afferents are already maximally recruited in the absence of peripheral sensitization (i.e., "floor effect"). Against such a proposal, our observed change in N2 latency from 35 to 38.5 and 42°C is almost exactly as predicted by changes in stimulation duration accompanying the increase in baseline temperature (i.e., nominal change in N2 latency predicted by a change in stimulus duration 35 to 38.5°C = −50 ms, actual change = −59 ± 25 ms; nominal change in stimulus duration from 35 to 42°C = −100 ms, actual change = −88 ± 30 ms; values are shown as averages ± standard deviations). Additionally, a recent study reported similar reductions in N2 latency (341 ± 90 ms – 285 ± 34 ms) with CHEPs baseline temperature increases from 35 to 40°C (Nakata et al., 2018), albeit non-significant. Overall, this suggests that similar populations of type II AMH nociceptors are recruited, across baseline temperatures (i.e., under control conditions).

These observations are limited to the temporal representation of the vertex N2P2 waveform. Time-frequency analyses may reveal non-phase locked responses that correspond with behavioral evidence of primary hyperalgesia. While stimulation conditions were randomized, capsaicin exposure always followed a recording session without capsaicin. This was done to avoid carry-over effects of capsaicin but may have influenced the findings. However, randomization of recording sessions would not overcome the inability to successfully blind participants to the perceptual effects of capsaicin, a known limitation of the capsaicin model. Previous studies have demonstrated fair to excellent test-retest reliability of CHEPs N2 latencies from cervical dermatomes (Kramer et al., 2012b) and lumbar dermatomes (Rosner et al., 2018), providing further confidence that our observed reductions in N2 latencies were due to the effects of capsaicin. Finally, a relatively low number of subjects (n = 12) may have contributed to type II error in relation to some of our observations (e.g., changes in amplitude). While our findings are limited to a small sample size ($n = 12$), we demonstrated the ability to successfully replicate our findings with a separate cohort of six participants. Nevertheless, the effect of capsaicin on N2 latency was robust.

CONCLUSION

In conclusion, capsaicin sensitization resulted in significant reductions in N2 latency when contact heat was delivered from a conventional baseline temperature (35 and 38.5°C). This effect is attributed to a reduction in activation threshold of type II AMH nociceptors and stimulation between 35 and 42°C, as stimulations from 42°C baseline were unchanged by capsaicin. CHEPs may be useful as a measure of peripheral sensitization related to the topical application of capsaicin, aiding in the evaluation of pain mechanisms.

DATA AVAILABILITY STATEMENT

The original data (raw EEG traces) are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by local ethics boards of the University of British Columbia and the University of Zurich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors assisted in the interpretation of the data, and the writing and editing of the manuscript. JH collected the data. CJ performed the original analysis and created the figures. LL collected the additional dataset and performed subsequent re-analysis.

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Emotion Measurements Through the Touch of Materials Surfaces

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The emotion generated by the touch of materials is studied via a protocol based on blind assessment of various stimuli. The human emotional reaction felt toward a material is estimated through (i) explicit measurements, using a questionnaire collecting valence and intensity, and (ii) implicit measurements of the activity of the autonomic nervous system, via a pupillometry equipment. A panel of 25 university students (13 women, 12 men), aged from 18 to 27, tested blind twelve materials such as polymers, sandpapers, wood, velvet and fur, randomly ordered. After measuring the initial pupil diameter, taken as a reference, its variation during the tactile exploration was recorded. After each touch, the participants were asked to quantify the emotional value of the material. The results show that the pupil size variation follows the emotional intensity. It is significantly larger during the touch of materials considered as pleasant or unpleasant, than with the touch of neutral materials. Moreover, after a time period of about 0.5 s following the stimulus, the results reveal significant differences between pleasant and unpleasant stimuli, as well as differences according to gender, i.e., higher pupil dilatation of women than men. These results suggest (i) that the autonomic nervous system is initially sensitive to high arousing stimulation, and (ii) that, after a certain period, the pupil size changes according to the cognitive interest induced and the emotional regulation adopted. This research shows the interest of the emotional characterization of materials for product design.

Keywords: touch, emotion, material, dilation of the pupil, explicit and implicit measures

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INTRODUCTION

The touch is an essential sense to the human because it allows the contact with our environment, the perception of wind, humidity, temperature changes, relief, roughness, softness, grip (Barnett, 1972). The touch is the most developed sense at birth (Field, 2001). Various studies have shown the influence of massage on brain development and improvement of visual function in premature rats, primates and humans (Stack and Muir, 1990; Field, 1998; Kaffman and Meaney, 2007; Guzzetta et al., 2009), with effects after the first week of stimulation in puppies (Sale et al., 2004). The lack of caresses is known to be a cause of death in orphaned babies (Spitz, 1945) and in baby monkeys (Harlow and Harlow, 1962). Study on maternal care of baby rats established that adult rats descended from a mother who gave numerous licks/groomings showed lower levels of fear reactivity than rats descended from a mother who dispensed very little (Menard et al., 2004;

Dunbar, 2010). The pleasant properties of caresses on cats, dogs, humans have often been demonstrated (Harlow, 1959; De Waal, 1989; Lindgren et al., 2010). The therapeutic properties of touch are well known, and it seems that the touch has a significant impact on the neuro-hormonal system (Bush, 2001). Different hormonal changes have been observed in tactile stimulations: change in the rate of cortizol in children after a simple contact with the skin of their mother, change of insulin levels with significance effects on type 2 diabetes, secretion of oxytocin during a pleasant touch (Feldman et al., 2010; Baldini et al., 2013; Clermont, 2018). Human skin is considered as a social organ (Löken and Olausson, 2010). Recent studies suggest (i) that the degree of allowed touch can predict the closeness of a relationship (Suvilehto et al., 2015), and (ii) that the degree of actual touch can predict functional connectivity of the social brain (Brauer et al., 2016). Other studies on social relation showed that a caress activates different emotional cerebral areas, depending on whether participants believe it to come from a person of the same or of the opposite sex (Dolinski, 2010; Gazzola et al., 2012).

The psychophysical dimensions of touch have also been studied (Taylor and Lederman, 1975; Jones and Lederman, 2006; McGlone and Reilly, 2010; Zahouani et al., 2013; Abdouni et al., 2017, 2018). The "epicritical" sensitivity corresponds to the fine and discriminative touch (shape, contours, texture, and relief) (Mountcastle, 2005), while the "protopathic" sensitivity corresponds to the cutaneous sensitivity triggered by strong stimulation, like temperature. The "protopathic" sensitivity generates a defense reaction of the body (Melzack and Wall, 1965).

The "epicritical touch" is achieved by Meissner's corpuscles and Merkel's receptors. Meissner's corpuscles are speed detectors that encode motion. Merkel's receptors are sensitive to intensity, pressure and temporal information on stimuli. The "protopathic touch" is achieved by Pacini's corpuscles and Ruffini's receptors. Pacini's corpuscles are sensitive to vibrations and record temporal information on stimuli. Ruffini's receptors are sensitive to the stretching of the skin. The skin also includes thermoreceptors, nociceptors and itch receptors that are sensitive to thermal sensations, pain and skin irritation and itching (Nordin, 1990; Misery and Ständer, 2010; Misery, 2014). Touch also involves proprioceptors, which are sensitive to changes of position and angular velocity of an articulation, tendon. There are three main types of proprioceptors: free nerve endings, Golgi receptors and Pacini corpuscles (Hasan, 1992; Edin, 2001).

Okamoto et al. (2012) have identified five dimensions of the "epicritical" touch that affect our tactile perceptions: hardness *(hard, soft),* temperature *(hot, cold)*, friction properties *(wet, dry, sticky, slippery)*, fine roughness *(rough, smooth)* and macro roughness *(uneven, relief).* Lederman and Klatzky (1987) have defined the gesture adapted to the tactile characterization of objects and surfaces. Gibson (1962) and Wall (2000) propose to distinguish the "Active" or voluntary touch, and the "Passive" or involuntary touch. During an "Active" touch, the mechanoreceptors of human skin treat tactile, proprioceptive and kinesthetic information which are relayed to the central nervous system to produce the emotional and sensory quality of the material. Some studies have focused on the study of perceptive sensory or emotional lexicons (Melzack, 1975; Essick et al., 1999, 2010; Cardello et al., 2003; Guest et al., 2011). Other studies have investigated the links between physical properties of materials and associated hedonic sensations (Chen et al., 2009: Datta, 2016). These different studies offer a better understanding of the emotional aspects of materials in order to master their emotional impact in a sensory design process.

The aim of this paper is to investigate pupil size variation in response to touch of different materials. It is the first study relating emotional touch with pupillometry. After describing the link between touch and emotional development, the experimental procedure is detailed, and the results are discussed.

TOUCH AND EMOTIONAL DEVELOPMENT

Studies on emotional touch have advanced through the study of a patient (GL) with Guillain-Barré syndrome (Forget and Lamarre, 1987). This patient had lost almost all large myelinated afferents, resulting in a total deficit of discriminative touch, over the whole of the body. Despite this deficit, she was able to describe the movement of a soft brush on her arm, as a light, pleasant and gentle touch. A little before, Zotterman (1939) had identified non-myelinated C-Tactile fibers (CT) in cats. These fibers have also been found in the hairy skin of mammals (Leem et al., 1993; Li and Ginty, 2014; Liljencrantz and Olausson, 2014; Rutlin et al., 2014; Walsh et al., 2015; Moayedi et al., 2016). The qualitative feelings of affective stimuli are comparable in hairy and glabrous skin. Recent studies suggest that different CT fibers have been found in the glabrous skin and have different biochemical and structural characteristics (Nagi and Mahns, 2010, 2013; Djouhri, 2016). The hedonic feelings felt with the fingertips still remains to be explained. Recent studies have identified MrgprB4 neurons in mouse as being involved in the pleasure felt during massage. In the experience realized, the MrgprB4 neuron was only activated the mouse was stroked with a brush. Results suggest that CT fibers with MRGPRB4 have distinct sensitivity to other anatomically similar CT neurons with receptors (MRGPRD) sensitive to unpleasant stimulation (Vrontou et al., 2013). This new knowledge could partly explain the gentle touch felt by the extremity of the finger.

A study realized on healthy subjects by Functional magnetic resonance images (fMRI) show that soft brush stroking activates the somatosensory areas S1 and S2, as well as insular cortex, notably the posterior part of the contralateral insular cortex (Olausson et al., 2002). S1 and S2 receive fibers Aβ projections and are known to play crucial roles in discriminative touch. When similar brushing stimuli are applied to GL, no activation is found in the somatosensory areas when the posterior insular region is activated (Olausson et al., 2010). The unmyelinated CT afferents, therefore, probably have excitatory projections mainly to emotion-related cortical systems such as the insular cortex (Vallbo et al., 1993; Vallbo et al., 1999). Other studies (Rolls et al., 2003) showed that the orbitofrontal cortex is involved in representing both positive and negative affect produced by touch, as it is the case with a stimulation through other sensory modalities (Rolls, 2000).

The emotional response triggered by a stimulus can be studied according to its three components: the expressive component (or behavioral response) measured by electromyogram of facial muscles, the cognitive component (feeling experienced) evaluated by self-assessment questionnaires, and the physiological component (or autonomic activity). Recent technologies allow now scientists to measure the emotions more accurately. For instance, in an array of pictures, those inducing fear (e.g., snakes) are located faster than the others (Öhman et al., 2001). Moreover, between 60 and 100 milliseconds after displaying an unpleasant stimulus, those inducing fear produce larger amplitude of visual evoked potentials than the others (Stolarova et al., 2006).

The first data showing a clear correlation between pupil diameter change and emotion were published in the sixties (Hess and Polt, 1960). Later, Bradley et al. (2008) have used emotional images to study their effect on the pupillary response. They divided pictures of the International Affective Picture System (IAPS; Lang et al., 2005) into three equal parts being considered, respectively, as pleasant, neutral and unpleasant. The results showed that the diameter of the pupil is significantly affected by the emotional pictures: the pupil becomes more dilated with emotional pictures, whatever its valence (i.e., pleasant or unpleasant). Additionally, Bradley et al. (2008) reported that the pupil diameter changes are correlated with changes in the conductivity of the skin, but not with the heart rate. This is consistent with the idea that the pupil diameter reflects the activity of the sympathetic nervous system. Recently, other studies suggest that non-visual emotions can also increase the diameter of pupils. This has been observed with participants listening to emotional sounds (Partala and Surakka, 2003; Babiker et al., 2013) or testing emotional products (Lemercier et al., 2014). In neuropsychology domain, by studying the effect of emotional stimuli on pupil diameter of people with Parkinson's disease, Dietz et al. (2011) have found a normal sympathetic excitation to affective stimuli (indexed by pupil diameter), but no oculomotor differences.

The pupillary response reflects the activity of the autonomic nervous response, especially the parasympathetic and sympathetic systems (Charier et al., 2017). The parasympathetic system innervates the sphincter pupillae and controls the pupil constriction, whereas the sympathetic nervous system causes the excitation of the dilator pupillae (Beatty and Lucero-Wagoner, 2000). Initially, the major role of these muscles is to adjust the amount of light allowed to enter the eye (Ellis, 1981). Recently, a review of 134 studies (Kreibig, 2010) has shown that many theories agree on the relationship between emotion and the organization of autonomic nervous system activity. In this way, many authors propose to adopt an observation of the results according to the type of emotion examined. This is consistent with the results of Bradley et al. (2008). An increase of pupil diameter and sweating is observed in pleasant and unpleasant conditions, whereas the heart rate slows down for negative stimuli and increases with neutral and pleasurable condition. Other researchers have studied heart rate variability in different emotional states (Onorati et al., 2013; Park and Thayer, 2014).

It is now well-known that touch involves a sensory and emotional integration (Chaplan et al., 1994; Armaied et al., 2005; Rolls and Kesner, 2006; Spapé et al., 2015; Schirmer and Adolphs, 2017). Nevertheless, few studies have examined the activity of the autonomic nervous system during an exploration by touching a surface. Thus, the present study proposes to measure the emotional touch of different surfaces with explicit (verbal rating scale) and implicit (pupillometry) measures. We expect that the tactile exploration of an emotional material will increase the activity of the dilator muscle. Therefore, pupil diameter is supposed to increase with material surfaces with high emotional Intensity, regardless their hedonic valence.

EXPERIMENTAL PROCEDURE

Participants and Materials

A preliminary study was conducted to select test materials, within a library containing 50 different samples (*wood, fabrics, furs, skins, metals, plastics, slimes, sandpaper)*. This library was created according to the recommendations on the representation of the pleasant touch specified in the literature (Greenspan and McGillis, 1991; Francis et al., 1999; Rolls et al., 2003; Thieulin, 2017). Six participants were asked to estimate the emotional valence and intensity of the surfaces, and two set of six materials were selected. The set 1 contains six surfaces obtained by 3D printing of six different neutral materials. Three of them are made of 100% polylactic material (green, pink, turquoise), and the others contain 50% of wood, copper and titanium powder, respectively. The measured roughness coefficients of these samples range from 0.255 to 0.417. The set 2 is made of six emotional surfaces. Two of them are considered as pleasant (very soft velvet and artificial fur). The three others are different grades of sandpaper, with an increasing roughness, i.e., N1 (slightly rough), N2 (moderate rough) and N3 (very rough). They are considered as unpleasant.

A panel of twenty-five students, 12 men and 13 women aged from 18 to 27, was selected. According to the "Edinburg" test which allows calculating the coefficient of laterality (Q.L.) on the basis of the examination of 12 gestural tasks (Oldfield, 1971), the panel was found to be right-handed, except for a female subject. According to the "Von Frey" test, which measures the changes in tactile sensitivity by using five calibrated filaments (Von Frey, 1896), all participants have a normal tactile perception. Finally, the emotional state of the participants before the test was estimated by using the questionnaire of the "HAD – Hospital Anxiety and Depression scale" (Zigmond and Snaith, 1983). Four subjects presented a score above the pathological limit. Therefore, the HAD scores were introduced as covariate in our analyses. Since these data were found to induce no measurements bias, the twenty-five students were kept for the test.

Procedure

Emotion outcome was assessed (i) via a self-report judgment (explicit measure), to collect information on intensity and valence

(Russell, 1980), and (ii) via measurements of the autonomous nervous system using a pupillometer. Since the works of Osgood (1969) and Russell (1980), stimuli can be characterized by two dimensions, valence and intensity. Valence refers to the hedonic nature of information on a continuum ranging from "positive, pleasant" to "negative, unpleasant" while the intensity corresponds to the level of physiological activation provoked by emotional information on a continuum ranging from "calm" to "excited". Many authors (Bradley et al., 2008) have shown that pupillary responses might serve as a reliable index of emotional intensity and other works have shown the interest of collecting the emotional value of a material (Bertheaux et al., 2018). This physiological response is considered as more automatic and implicit than explicit, verbalized self-report measures. Pupil diameter is modulated by emotional intensity (linked to somaesthetic cues). Studies comparing and correlating emotional responses about their peripheral physiological mechanisms and self-report judgment, are limited in number.

The participants were sitting on a comfortable chair, the arms resting on a table to limit the movement of the body, in an artificially lighted room with a small opening on the outside. Luminance measurements gave values ranging from 240 to 250 Lux. A 850 × 850 mm white wooden tray with a target point in its center was placed at 40 cm in front of the participants. This experimental equipment was used to focus the gaze toward a target point to facilitate the measurement of the pupil and to avoid any distractions. To perform a blind experiment, the materials were placed in an experiment box with 6 materials in 6 housing spaced 25 mm. The box dimensions were 700 mm long, 140 mm high and 200 mm deep. The samples were 70 × 70 × 5 mm to allow exploration of the surface with 3 fingers per tangential and circular touch. Randomly ordered set 1 and 2 were presented successively to the participants.

During the test, an experimenter was placed behind the subject so that the participant was not tempted to look at him during the answers. He described each step to the participant who executed the experiment. A second experimenter, located beside the participant, registered markers in order to sequence each measurement step. **Figure 1** gives the different steps of the procedure. The first step consisted in a blind touch during 15 s of a randomly chosen material of the set. This step erased the "surprise" effect, and the associated data are not processed. It was followed by a recorded "Rest phase" of 30 s, which was used to define the initial pupil diameter of the participant d_0. Then, participants silently touched each material during 15 s with the dominant hand. After this touching period, the experimenter asked them about his feelings and noted their answers during 30 s. Valence was assessed using a scale from –4 (very unpleasant) to +4 (very pleasant), and intensity is ranged from 0 (very calm) to 5 (very excited).

The scales used for valence and intensity are adapted from the SAM scale (Self Assesment Mankini), which proposes to measure the emotion on three dimensions: pleasure (valence), excitation (intensity) and dominance (Bradley and Lang, 1994). During the "Discussion Phase", the participant said whether the sample was pleasant (yes or no) and indicated his feeling on the valence scale (−4 to 4). Then, the participant said whether he has felt an emotion (yes or no), and quantified it with the intensity scale (0 to 5). A written example is shown in **Table 1**.

Pupil diameter measurements were performed at 60 Hz with an ISCAN-ETL-100H pupilometer device connected to an infrared camera. The size of the pupil in pixels is detected in the vertical and horizontal directions, and the mean value at time t gives de pupil diameter d(t).

RESULTS AND DISCUSSION

Questionnaire

Figure 2 gives the histograms of emotional values collected by the questionnaire for two samples, "Green polylactic (PLA)" (**Figure 2A**) and "synthetic fur" (**Figure 2B**). In **Figure 2A** the values are clearly distributed around a mean value of 0.6 (intensity) and 1.76 (valence). The emotional value of this sample is considered as "neutral". In **Figure 2B**, the intensity values are highly positive, between 3 and 4, with a mean value of 3.12, and the valence is mainly positive, with a relatively high mean value of 3.84. The emotional value of this sample is therefore considered as "pleasant". However, it can be observed in **Figure 2B** that two participants have considered the synthetic fur as very unpleasant, with two ratings at −3. This can probably be explained by the cultural background of these two participants who raised in an environment with wild animals. Actually, the furry animals are often considered as pleasant. Often during our childhood, we

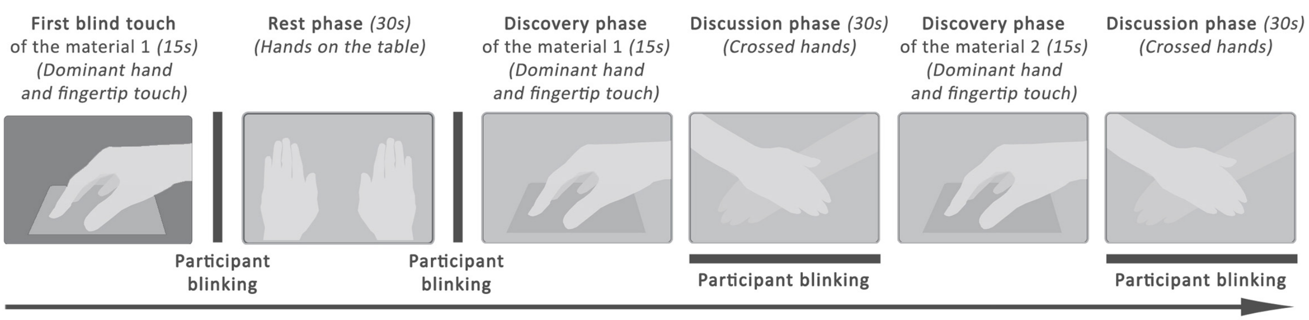

FIGURE 1 | Experimental procedure applied on each set.

TABLE 1 | Sample of survey used in the subject assessment.

Sample 1:	*Would you say the sample is pleasant?*		*Did you feel an emotion in contact with the sample?*	
Type of material	*Yes* ☐	*No* ☐	*Yes* ☐	*No* ☐
	On a scale of −4 to 4:		*On a scale of 0 to 5:*	
	−4 −3 −2 −1 0 1 2 3 4		*0 1 2 3 4 5*	
	How would you describe your emotion?			

experiment the soothing and relaxing effect of touch with a cat, a dog, a teddy bear . . . (Servais, 2007). It does not represent a danger. Nevertheless, the two students lived in a country where animals are dangerous, so that they did not consider the fur as pleasant as the other students.

Considering all the participants, the mean value of the verbalized valence was found to be 2.74 ± 1 for the two pleasant materials (very soft velvet and artificial fur), -0.41 ± 0.55 for the three unpleasant materials (sandpapers), and 0.77 ± 0.07 for the seven remaining neutral materials. A Friedman test on the valence ratings showed that these three conditions of emotion were significantly different ($\chi^2 = 50$, $p \leq 0.0001$), and *a posteriori* Wilcoxon analysis showed significant differences between the three dimensions ($p < 0.0001$). Similarly, the mean intensity ratings for the pleasant, unpleasant and neutral touch stimulus across all subjects were, respectively, 3 ± 0.16, 2 ± 0.10, and 1.9 ± 0.17. A Friedman test on these intensity ratings showed that the three conditions of emotion were significantly different ($\chi^2 = 48$, $p \leq 0.0001$). *A posteriori* Wilcoxon analysis showed significantly higher score for pleasant stimuli compared to neutral and unpleasant stimuli ($z = 4.37$, $p \leq 0.0001$ and $z = 4.37$, $p = 0.0001$, respectively), and the pattern of results indicated higher mean intensity score for negative stimuli compared to neutral touch ($z = 4.13$, $p = 0.0001$). No specific gender differences appeared and the HAD score had no influence on the scales scoring.

Pupil Diameter Change

A cleaning algorithm has been applied to all the recorded diameters to detect blinks, absence of measurements, and measures considered aberrant (pupil size too high). After detection, the algorithm uses a numeric interpolation and replaces this data with a corrected data bridge that covers the mapped interval (Schlomer et al., 2010). For each material and for the rest phase, the recorded pupil diameters were exploited for 2 s. This duration was defined according to the work of Bradley et al. (2008), which shows that the constriction of the pupil intervenes from 0.6 to 1.6 s after the presentation of an image (emotional stimuli).

The data processing was finally performed by calculating the relative evolution of the pupil diameter of each subject, for each material, during the discovery phase, as $[d(t)-d_0]/d_0$. The d_0 value is obtained by averaging the pupil diameter values during the last 2 s of the rest phase for each subject. Participants observed two periods of Rest phase, one taken during the measurement of set 1 and the other during set 2. The d(t) value is the pupil diameter of the participant measured at time t during the first 2 s of the discovery phase.

Figure 3 shows the time and participant averaged pupil dilatations for all materials, classified from unpleasant to pleasant, together with the mean verbalized valence and arousal. According to the Bienaymé-Tchebychev Inequality Test, in the

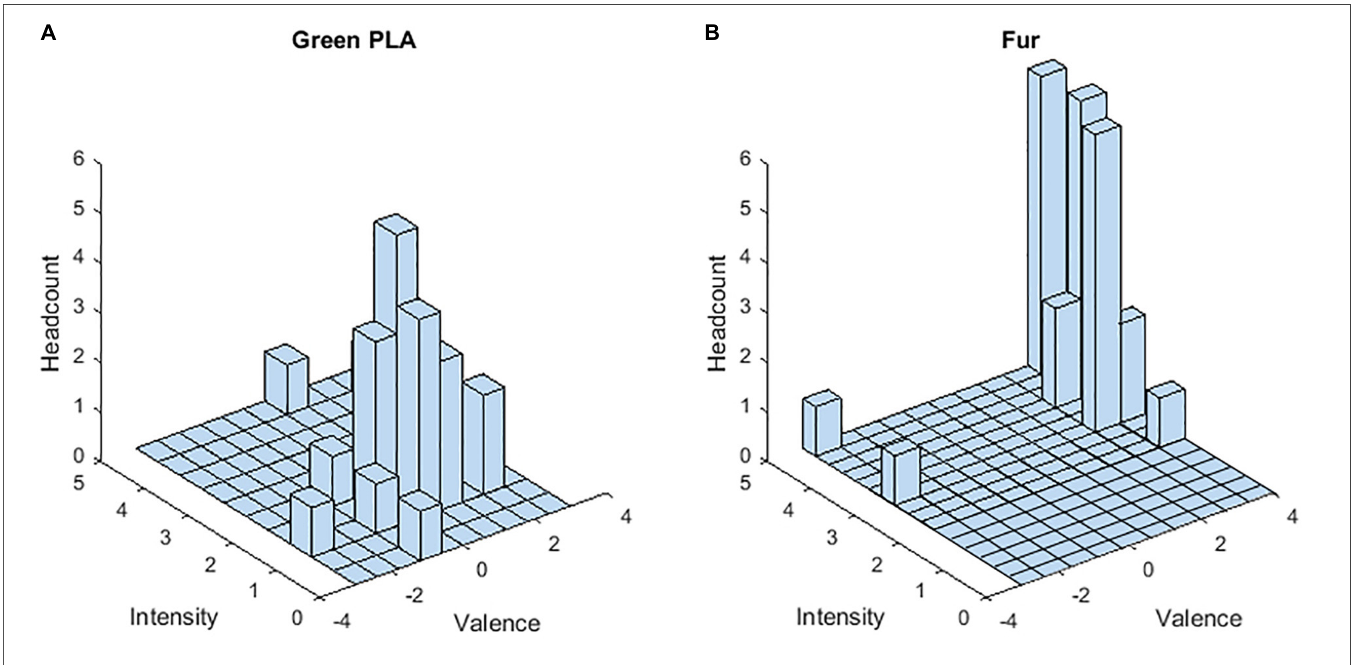

FIGURE 2 | Emotional values (valence and Intensity) of two samples. Histograms of Green PLA **(A)** and Fur **(B)** as a function of Intensity and Valence.

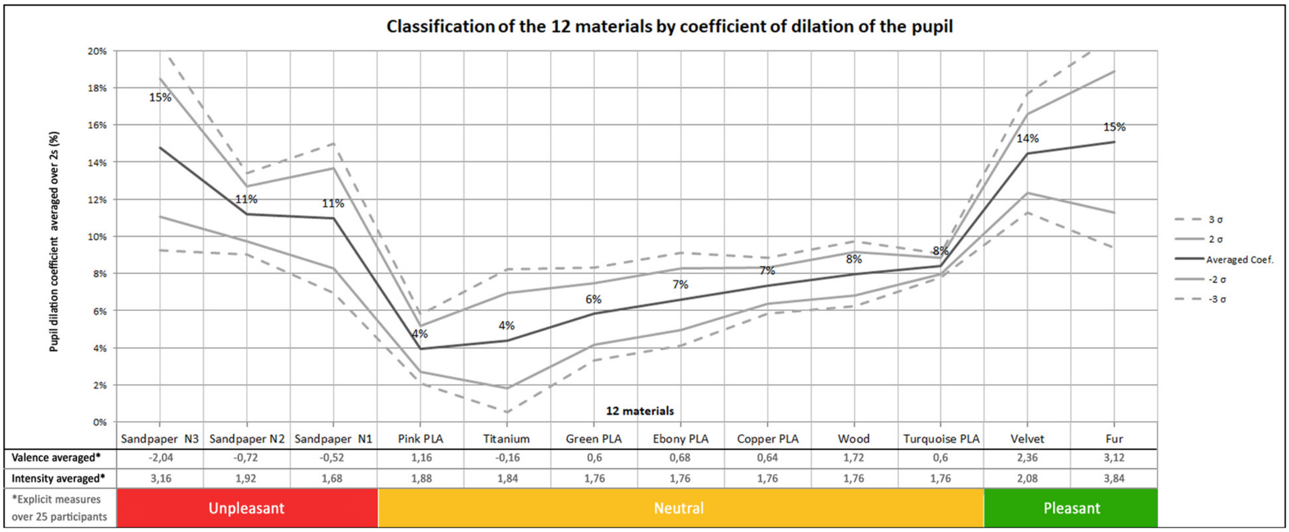

FIGURE 3 | Classification of materials by coefficient of dilation of the pupil on 3 conditions: unpleasant, neutral, pleasant.

case where the data do not follow a normal law, the probability that the random variable will be realized in interval ±2 σ is 75%, and becomes 89% in the range of ±3 σ. It can be observed in this figure that high emotional materials present larger pupil dilatations than neutral materials, but that pupil dilations for unpleasant and pleasant materials are very similar.

Figure 3 suggests that our statistical analyses can be performed with the following three classes of materials:

- Three Unpleasant: sandpapers from N1 to N3;
- Seven Neutral: all PLA, Titanium and Wood;
- Two Pleasant: Velvet and Fur.

We performed the Shapiro–Wilk test on this dataset. At 5% risk, our results showed that our data don't follow a normal distribution. Therefore, all data were rank transformed (Conover and Iman, 1981) and submitted to an ANCOVA. The HAD score was used as covariate since previous studies showed that the level of mood can influence the processing of emotional materials (Mogg and Bradley, 1999; Mogg et al., 2000). We included in the present analyses the inter-subject factor "group" (male and female) and the within-subject factor "emotion" (pleasant, unpleasant and neutral). In addition, pairwise *post hoc* comparisons with the Bonferroni test and planned comparisons were performed when appropriate. The ANCOVA showed no effect of the HAD score on the overall results, but the "group" and emotion" factors were found to be significant.

The effect of emotion is significant [$F(2,24) = 10.87$, $p = 0.0004$]. **Figure 4** shows the pupil dilation coefficient of the participants during the discovery phase. These data are averaged over the three classes of materials: neutral, unpleasant, pleasant. The following observations can be made on this graph:

- The neutral materials lead to a lower pupil dilation than the pleasant [$F(1,12) = 146.07$, $p = 0.0001$] and unpleasant materials [$F(1,12) = 11.99$, $p = 0.004$];
- A constriction of the pupil is located around 0.05 s;
- After the constriction zone, the neutral curve is fairly constant in time, the pleasant curve increases during 0.5 s, and then stay roughly constant and the unpleasant curve stay constant during 0.5 s, before decreasing with greater variability on the end.

An observation conducted on the temporal data showed that the emotional conditions of pleasant and unpleasant materials become different from 0.50 to 2 s ($p = 0.03$).

The group factor (male and female) was found to also significant [$F(2,24) = 3.42$, $p = 0.04$]. The pupil is more dilated in women than in men under both pleasant and unpleasant conditions ($p = 0.05$ and 0.0001, respectively).

As shown in **Figure 5**, the pupil dilation coefficients of women are situated between 13 and 19% for the unpleasant and pleasant conditions, while they range between 4 and 6% for the neutral materials. The *post hoc* analysis showed a difference between unpleasant and pleasant ($p = 0.01$), unpleasant and neutral ($p = 0.001$) and pleasant and neutral ($p < 0.0001$) materials. The positive stimuli seemed to be the most emotional for women. In women, the curves showed that after 0.50 s the positive stimulus increased and the neutral and negative settled down.

The pupil dilation coefficients of men are depicted in **Figure 6**. They range between 2 and 12% for the unpleasant and pleasant conditions, and between 6 and 8% for the neutral condition. Furthermore, the curve presents much more variation than for women. The *post hoc* analysis showed a difference between unpleasant and pleasant ($p = 0.004$), unpleasant and neutral ($p = 0.009$) and pleasant and neutral ($p < 0.0001$) materials. During the 2 s observed, the neutral curve is nearly constant. The pleasant stimulus shows large oscillation with a first peak at 1 s and a second peak at 1.70 s. The negative stimulus is located above the neutral and below the

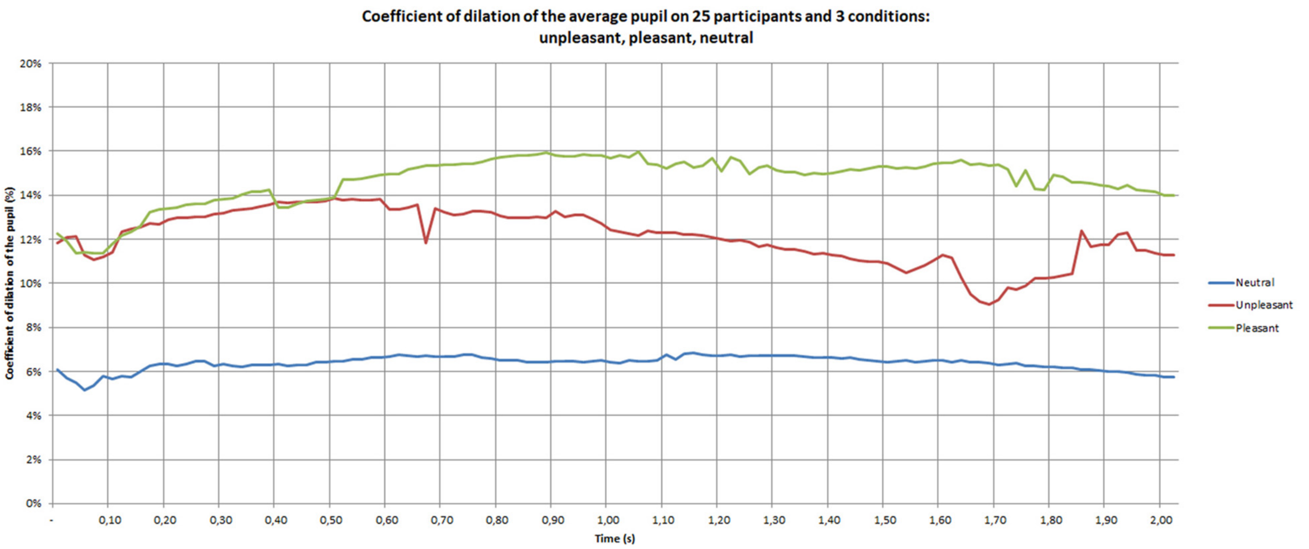

FIGURE 4 | Pupil dilation coefficient of the participants during the discovery phase.

positive during the first second, and then a sharp decreased occurs that places the negative stimulus below neutral and pleasant conditions. Pleasant stimuli seem to be the most emotional for men.

Figures 7–9 give the pupil dilation of men, women, and averaged, in the case of pleasant, unpleasant, and neutral materials. It can be observed in these figures that:

- for the pleasant materials: the pupil dilation is larger for women than for men, with similar time evolutions, but with similar curves slightly noisy in the men case (**Figure 7**);
- for unpleasant materials: the pupil dilation is greater for women than for men with different time evolutions: nearly constant for women, and decreasing after 0.70 s for men (**Figure 8**);
- for neutral materials: the pupil dilations are roughly similar for men and women (**Figure 9**).

In **Figure 10**, a Principal Component Analysis (PCA) classifies the materials according to the mean value of the pupil dilation. Principal component analysis is a method of eliminating bias. On the horizontal principal axis, which represents 93.10% of the values, the materials are clearly ordered according to their Intensity, from neutral to emotional. This ranking is close to the classification made by the participants using subjective measures. On the vertical axis, which represents 2.56% of the values, the ordering of the materials is more difficult to analyze.

DISCUSSION

The aim of this study was to evaluate pupillometry as a measurement technique for emotion. For this purpose, an experimental procedure has been developed, and the touch of different surfaces has been used as a stimulus. The results show clearly an increase in pupil diameter within the first 2 s of the touch. As observed by Bradley et al. (2008), the initial increase is followed at about 0.04 until to 0.10 s by a slow decrease. After, the averaged pupil dilation follows a similar type of curve whatever the emotional materials until a period of about 0.5 s. The general pattern of results indicate a larger pupil size dilation in response to both negative (unpleasant) and positive (pleasant) stimuli, when compared with the dilation induced by neutral stimuli. After this time period of 0.50 s, the emotional response takes different ways. The pupil diameter tends to decrease for negative stimuli, whereas it stays constant for positive stimuli.

Pupil diameter can be considered as a physiological marker of the autonomic nervous system. The size of the pupil is fixed by the relative activity of the two iris muscles, the sphincter and the dilator (Beatty and Lucero-Wagoner, 2000). While pupil constriction is maintained by parasympathetic activity, pupil dilation is essentially induced by the sympathetic pathway (Andreassi, 2000). Because the size of the pupil is modulated by the autonomic nervous system, our results suggest that this system reacts differently to emotional and to neutral stimuli. This pattern of results confirms many studies suggesting that emotional intensity during picture viewing, sound auditioning, or tasting, is associated with high pupil dilation (Partala and Surakka, 2003; Bradley et al., 2008; Kret et al., 2013; Henderson et al., 2014; Lemercier et al., 2014). Bradley et al. (2008) indicated that the dilation of pupil diameter covaried with other autonomic measures of intensity, such as the skin conductance, confirming that pupillary responses can be considered as a reliable index of emotional intensity. More recently, Laeng et al. (2016) showed that emotional music may reveal changes in the diameter pupil and that a neuromodulator role of the central norepinephrine system is involved in this phenomenon. To our best knowledge, nobody has undertaken any studies on the response of the autonomic nervous system to touch.

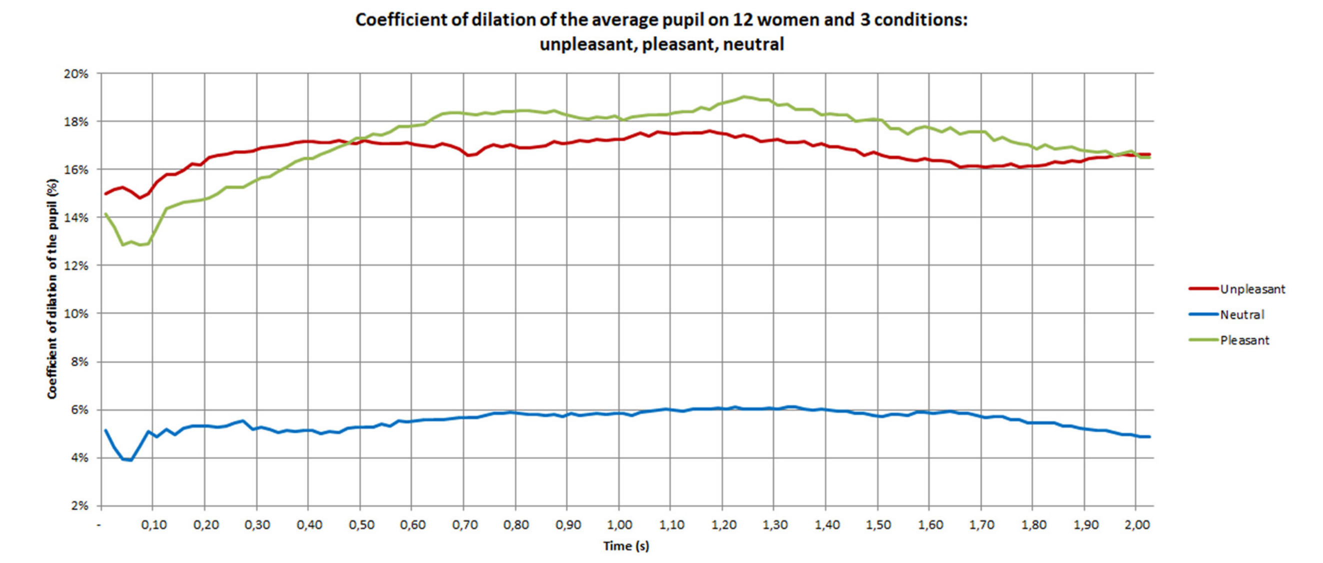

FIGURE 5 | Pupil dilation coefficient of women during the discovery phase.

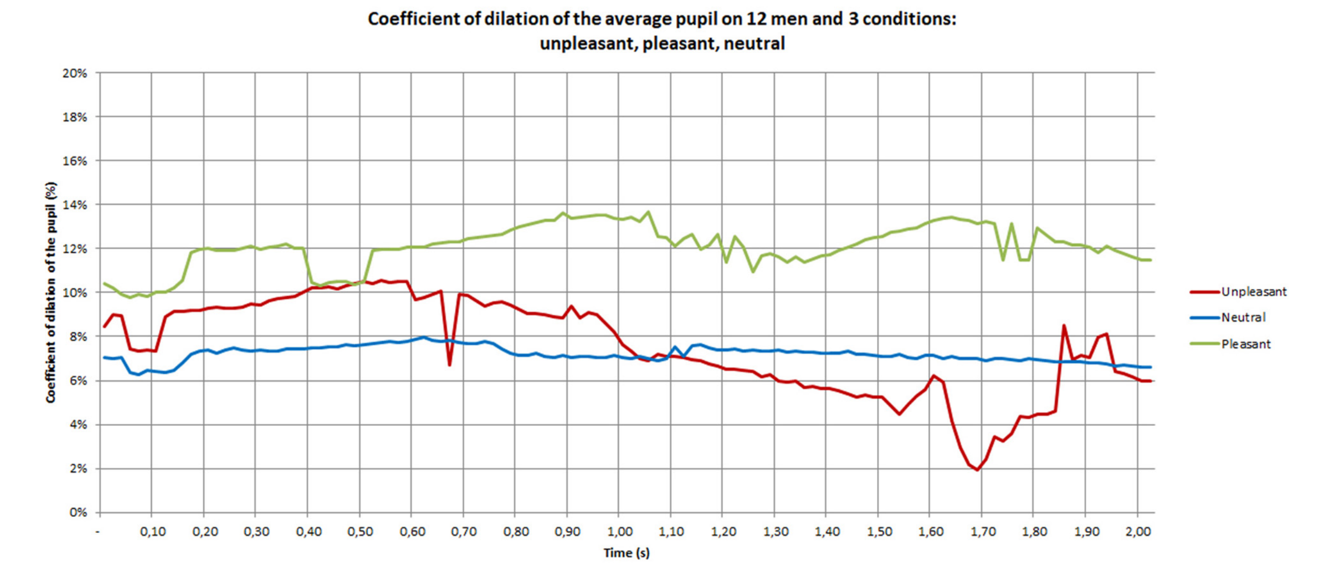

FIGURE 6 | Pupil dilation coefficient of men during the discovery phase.

Some studies indicated that changes in pupil diameter specifically occur within the first few hundred milliseconds after stimulus onset, with responses peaking after 1 to 2 s (Loewenstein and Loewenfeld, 1962; Andreassi, 2000; Beatty and Lucero-Wagoner, 2000; Nieuwenhuis et al., 2011). Beyond 2 s of regulation, we can also suppose larger pupil diameter. For example, Bradley et al. (2008) showed differences when participants viewed emotional or neutral pictures beyond 2 s. Partala and Surakka (2003) observed this effect with auditory stimuli. Our results show a dynamic pattern during the 2 s time period. Initially, unpleasant touch does not induce any difference compared to pleasant touch, but a difference can be observed after 0.50 s. In the same way, Partala and Surakka (2003) results showed that no pupil dilatation was observed before 0.40 s and that the maximum pupil dilatation was observed after 2 to 3 s. In addition, they showed that the time duration of the pupil diameter were somewhat different for female and male subjects. The positive stimuli provoke the strongest pupil dilations for female subjects, whereas the negative stimuli provoked the strongest dilations for male subjects.

As Partala and Surakka (2003), the present study showed an effect of gender but in a different way. The strongest pupil dilations appeared for both emotional conditions with women. This is constant with the duration time. For men, the emotional

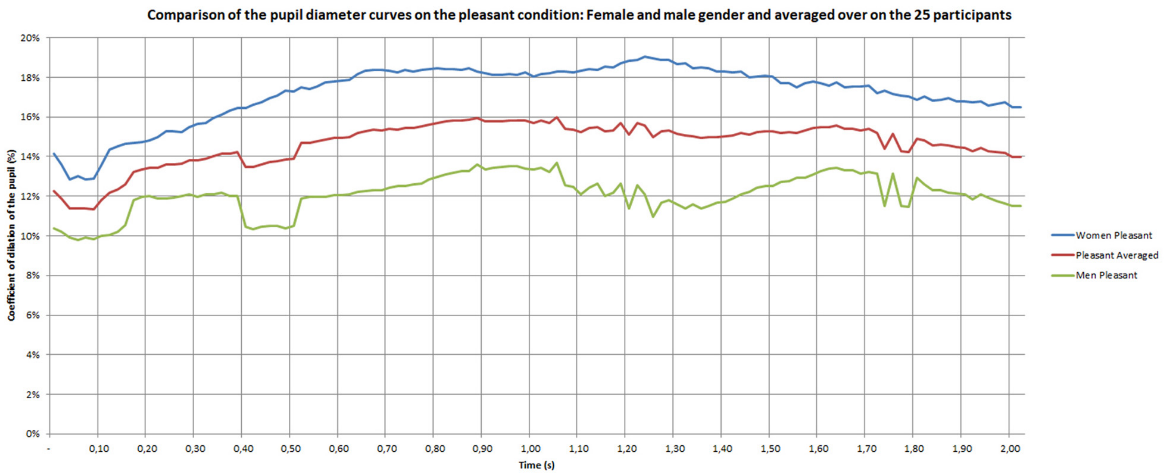

FIGURE 7 | Pupil dilatation coefficient for pleasant materials.

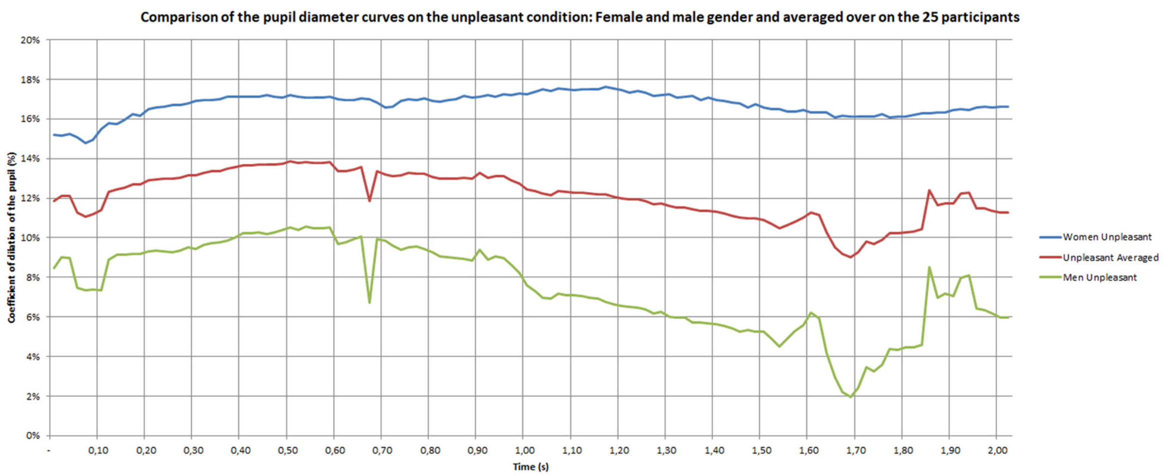

FIGURE 8 | Pupil dilatation coefficient for unpleasant materials.

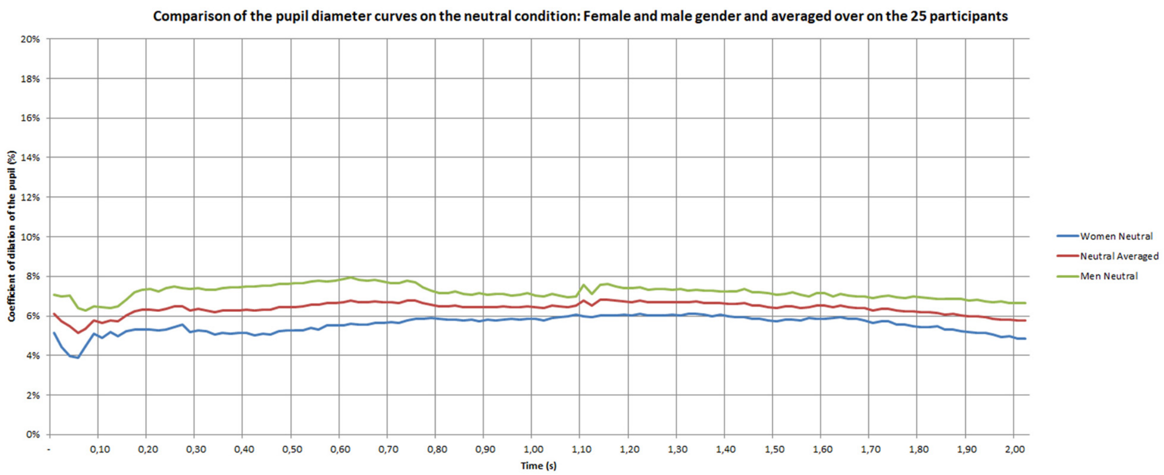

FIGURE 9 | Pupil dilatation coefficient for neutral materials.

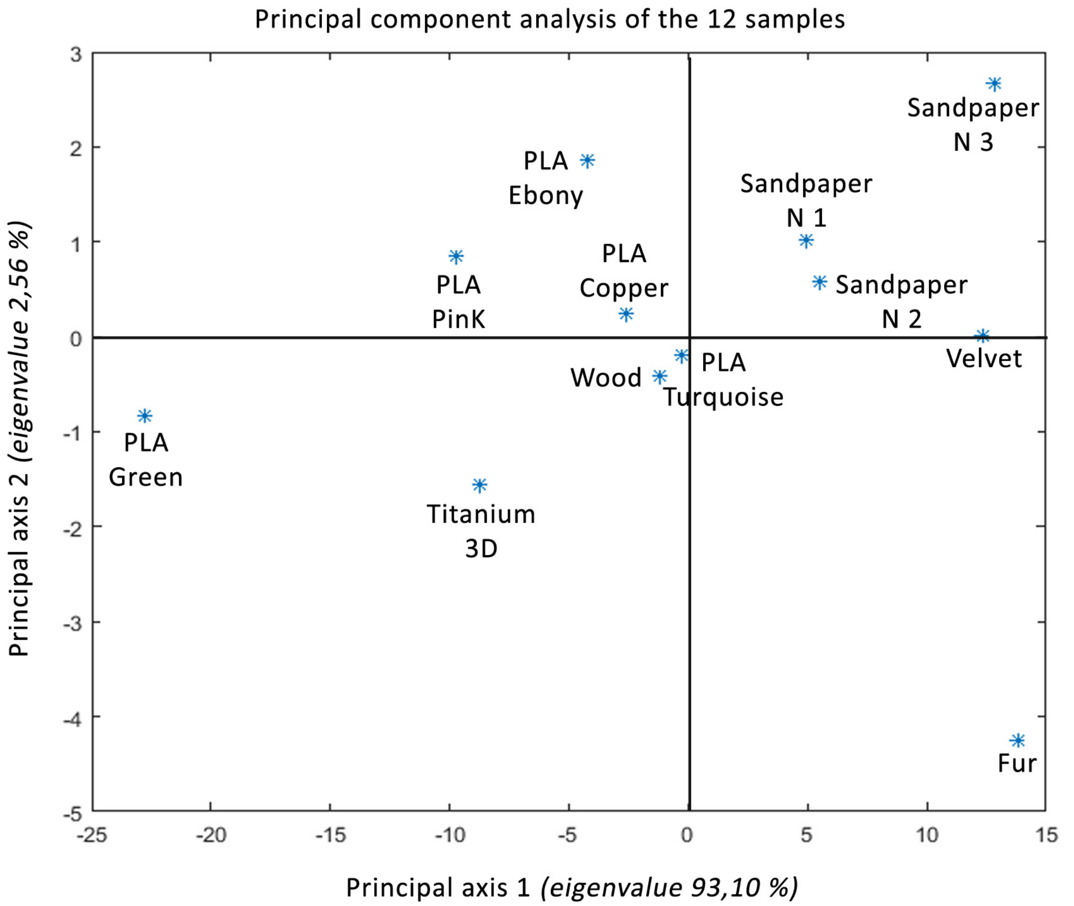

FIGURE 10 | Principal component analyzis of the twelve samples.

conditions induced a higher pupil dilations compared to neutral stimuli at the beginning. Nevertheless, a strongest decrease for negative emotion appeared with the time period. The explanation of a higher sensitivity in female participants could be explained by the difference of the skin thickness. It exceeds 60 microns for men (between 20 and 30 years old) and is often below 50 microns for women (Kawabe et al., 1985). For example, Peters et al. (2009) indicate that women can perceive finer surface details than men, and that tactile perception is improved with decreasing finger size (Van Boven et al., 2000; Goldreich and Kanics, 2003, 2006). An explanation of this phenomenon of better perception in women comes from the high density of Merkel's receptors and Meissner's corpuscles due to the small size of their fingers (Dillon et al., 2001; Peters et al., 2009). Other differences were found between men and women, like variability of vibrotactile detection thresholds, the volume of the area of contact with the material and a higher density of ridges in the fingerprint (Gutiérrez-Redomero et al., 2011; Venkatesan et al., 2015).

In the pain studies, many authors showed that the threshold of nociception by pressure decreases with age, especially in men. In contrast, age seems to have no effect on thermal sensations (Pickering et al., 2002). Another study showed that the temporal sum of mechanically evoked pain is seen with higher scores in women than in men (Sarlani and Greenspan, 2002). Studies of pupil changes due to painful pressure stimuli showed that increasing pupil diameter was a highly significant indicator of pain intensity. In this domain, female subjects show greater dilation than men at high pressure levels (Ellermeier and Westphal, 1995). These data lead us to the conclusion that the pupil dilation seems differently influenced by pain or emotion following the gender.

From a cognitive approach, Bayer et al. (2011) indicated that pupillary responses are sensitive to both task load and emotional content. Kuchinke et al. (2007) showed that word frequency significantly affected pupil dilation. The pupil diameter appeared to increase for low frequency words certainly because this type of words induced a more important cognitive load. In addition, cultural aspects are important in the touch of materials. This was demonstrated by Fisher (2004) in a study which suggests that consumer perceptions of plastics are physical and emotional. This researcher considers that the properties of plastics are "humanized" by different industrial processes making this material harmless, sensual and familiar unlike the animal or natural properties of some materials who remind us to our natural environment that can arouse more excitement. The appreciation of these materials varies according to the context, the emotional charge produced by its visual and tactile properties (Gibson, 1977) or cultural aspects due to habits. For example, sandpaper is mainly used by men in construction; manufacturing and its surface appearance may seem more familiar to them. Therefore, pupil dilation may reflect the time course of cognitive and attentional mechanisms inherent in emotion processing. Therefore, we can imagine that the pupillometry informs us as an emotional intensity (Rolls et al., 2003; Bradley et al., 2008) and can allow to show a pattern of results, with increase and decrease regulation (Urry et al., 2009), as it is the case in our study.

There is some evidence that self-report emotional answers vary with certain physiological changes associated with emotion (Levenson, 1992). In our study, we show that the materials are subjectively classified in the same order as the classification of the coefficient of dilation observed for the 12 materials. Thus, the main axis 1 seems to correspond to the bodily excitation of the tactile stimulus (Intensity). Nevertheless, the ratings of intensity showed that negative and positive stimuli were experienced as differently arousing. Our pattern of results justifies the use of verbal response in complement with physiological data. On one side, unpleasant touch was assessed as significantly less arousing than pleasant touch. On the other side, the positive intensity effect manifested specifically later during the pupillary response compared to the negative intensity effect. In accordance with subjective ratings, increasing positive emotions led to the most prominent pupil size enlargements during 2 s. These results confirmed that pupil diameter was modulated by the level of emotional intensity. Results suggested that pupil responses reflected the time course of the intensity perceived. According to Gross (1998), emotion regulation refers to both implicit, explicit physiological, behavioral and cognitive processes. The inclusion of multiple measures of autonomic intensity with subjective and behavioral emotional ratings might help to understand effects reflecting changes in emotional Intensity and cognitive demand.

In sum, the present study opens new research avenues. Our data evidence that the pupillary response in accordance with subjective data might include distinct temporal components reflecting emotional and cognitive regulation. It would be interesting to develop pupil diameter variation as a computer signal input. For example, it has been possible to develop signal analysis methods to detect successfully emotion from electrical activity of facial muscles.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author CBe, cyril.bertheaux@enise.fr.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CBe is doing his thesis at Université de Lyon, ENISE, LTDS, UMR 5513 CNRS on the emotional impact of touch and more particularly in the tactile exploration of materials. This research work aims to determine the emotional value of materials. For this multidisciplinary thesis, a partnership with the laboratories SNA-EPI Laboratory, EA 4607 (DC, pupil and ANS specialist) and CMRR, neuropsychology of the CHU Saint-Étienne (CBo, Thesis guide, specialist in emotion and cognition) was established to provide knowledge in metrology of the autonomic nervous system and in cognition. The rest of the management is made up of engineers researchers (RF, Thesis Director and RT, Thesis Co-director) and statisticians (J-CR, Thesis guide) who have contributed their skills to the various protocols and results collected. All authors contributed to all the steps until the writing of this article. Since 2016, several test protocols, data organization, interpretation, correction, mathematical and statistical treatments have made it possible to propose these results and manuscript revision, read, and approved the submitted version.

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A Multimodal Meta-Analysis of Structural and Functional Changes in the Brain of Tinnitus

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Brain imaging studies of tinnitus patients have revealed marked changes in brain structure and function, but there are inconsistencies in those findings. In this meta-analysis, we investigated concurrence across studies to clarify those abnormalities in brain structure and function in tinnitus. Neuroimaging studies published up to December 6, 2019 were searched in the PubMed, Web of Science, EMBASE, and Cochrane Library databases, Chinese Nation Knowledge Infrastructure, Chinese Biomedical Literature Database, the Chongqing VIP, and Wanfang Database. Study selection, quality assessment, and data extraction were performed by two independent researchers. Anisotropic effect size signed differential mapping (AES-SDM) was used to perform a multimodal analysis of available studies reporting whole-brain structural or functional data in tinnitus patients. There were 14 studies that met the inclusion criteria. The structural dataset comprised 242 tinnitus patients and 217 matched healthy subjects (HS), while the functional dataset included 130 tinnitus patients and 140 matched HS. Our analysis revealed structural alterations in the superior temporal gyrus, middle temporal gyrus (MTG), angular gyrus, caudate nucleus, superior frontal gyrus, and supplementary motor area, as well as functional differences in the MTG, middle occipital gyrus, precuneus, and right inferior parietal (excluding supramarginal and angular) gyri. The multimodal analysis revealed significant differences in the right MTG of tinnitus patients relative to HS. These findings suggest the involvement of the cortico-striatal circuits in the neuropathology of tinnitus.

Keywords: meta-analysis, tinnitus, multimodal, neuroimaging, signed differential mapping, voxel-based morphometry

INTRODUCTION

Tinnitus is characterized by the perception of sounds in the ears or head in the absence of any external stimulus (Wegger et al., 2017; Bauer, 2018) and affects ∼10–15% of the population (Shargorodsky et al., 2010; Baguley et al., 2013; Bauer, 2018). It often occurs in association with hearing impairment, insomnia, depression, anxiety, and difficulty in concentration, and significantly impairs patients' quality of life (Reynolds et al., 2004; Langguth et al., 2013; Zeman et al., 2014). Although phantom sounds are thought to originate in the cochlea, tinnitus is also related to maladaptive neuroplastic changes in the central nervous system as it often persists even after the auditory nerve has been severed (Berliner et al., 1992; Silverstein, 2001).

Structural and functional alterations in multiple auditory and non-auditory brain regions have been detected in tinnitus patients (Adjamian et al., 2009; Husain and Schmidt, 2014). For example, increased volume of gray matter (GM) in the bilateral superior temporal gyrus (STG), right middle temporal gyrus (MTG), and right supramarginal gyrus and decreased GM volume in the bilateral hypothalamus, left superior frontal gyrus (SFG), and right occipital lobe were observed in tinnitus patients (Boyen et al., 2013). On the other hand, some studies have reported no changes in GM volume associated with tinnitus (Landgrebe et al., 2009; Melcher et al., 2013). Furthermore, one morphometric study showed an increased GM volume in the right SFG (Schmidt et al., 2018), whereas the opposite was demonstrated by another voxel-based morphometry (VBM) study (Boyen et al., 2013). Besides anatomical changes, functional alterations have been detected in tinnitus (Chen et al., 2014, 2015; Han et al., 2018a), as evidenced by increased amplitude of low-frequency fluctuations (ALFF) in the right MTG, right SFG, and right angular gyrus and decreased ALFF in the left cuneus, right middle occipital gyrus, and bilateral thalamus (Chen et al., 2014). However, increased regional homogeneity (ReHo) in the frontal cortex (Chen et al., 2015) and decreased ReHo in the frontal gyrus (Han et al., 2018a) have also been detected in two different studies.

Although tinnitus is thought to involve many brain areas, the evidence on regional alterations has been inconsistent across studies (Boyen et al., 2013; Chen et al., 2015; Han et al., 2018a; Schmidt et al., 2018), possibly due to differences in sample size, demographic and clinical characteristics of patients, imaging modality, and analytical approach (Boyen et al., 2013; Allan et al., 2016; Schmidt et al., 2018). At present, little is known about the association between structural and functional changes, as there have been few multimodal studies. A previous meta-analysis of functional magnetic resonance imaging (fMRI), positron emission tomography, and single-photon emission computed tomography studies revealed an increased activity in several brain regions including right SFG, MTG, bilateral insula, inferior frontal gyrus, parahippocampal gyrus, and posterior lobe of the cerebellum and a decreased activity in the left cuneus and right thalamus (Chen et al., 2017). Cross-validation from structural and functional brain alterations is still required to confirm the reliability of these findings and better understand the cerebral characters of tinnitus.

Anisotropic effect size signed differential mapping (AES-SDM) is a method used for the meta-analysis of neuroimaging data. Unlike activation likelihood estimate and multi-level kernel density analysis that are based on regional likelihood or frequency of reported peak locations of significant activation clusters (Wager et al., 2007; Eickhoff et al., 2009), AES-SDM combines peak coordinates and statistical parametric maps and uses standard effect size, which allows an exhaustive inclusion and accurate estimations of studies (Radua and Mataix-Cols, 2009; Radua et al., 2012a, 2014). AES-SDM has high sensitivity, consistency, and a low rate of false positives (Radua et al., 2012a) as well as higher accuracy than other coordinate-based methods owing to increased reliability and validity of the neuroimaging data (Radua et al., 2012a).

We speculated that there is an overlap in the structural and functional changes in patients with tinnitus compared to healthy subjects (HS). In this study, we used AES-SDM to test this hypothesis by comparing GM volume and spontaneous activity reported in whole-brain VBM and fMRI studies.

MATERIALS AND METHODS

Search Strategies

A systematic search strategy was used to identify relevant studies. Two independent researchers (SC and JZ) performed a two-step literature search of the PubMed, Web of Science, EMBASE, and Cochrane Library databases, Chinese Nation Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), the Chongqing VIP (VIP), and the Wanfang Database (WF) to identify structural or functional imaging studies on tinnitus. The search was conducted up to December 6, 2019, with no time window specified for date of publication. The following English search terms were used: ("tinnitus" OR "acousma" OR "akoasm" OR "phantom sound" OR "auditory phantom sensation") AND ("magnetic resonance imaging" OR "MRI" OR "functional MRI" OR "fMRI" OR "voxel-based morphometry" OR "VBM" OR "voxelwise" OR "gray matter" OR "regional homogeneity" OR "ReHo") AND ("resting state"). This search strategy has been modified to be suitable for Chinese electronic databases. The reference lists of articles cited in reviews were manually checked for any studies not identified by our database searches. Corresponding authors were contacted by email or telephone if data were not available or if questions about the data arose.

Selection Criteria

The included studies met the following criteria: (1) original paper reported in English or Chinese viewed journal; (2) comprised patients diagnosed with subjective tinnitus and HS; (3) involved whole-brain structural or functional imaging of both groups; (4) results of x-y-z coordinates were reported in Montreal Neurological Institute (MNI) or Talairach coordination; and (5) a 1.5T or 3.0T MRI scanner was used.

The exclusion criteria were as follows: (1) it did not report a VBM comparison of GM volume, modulated GM concentration, ReHo between tinnitus patients and HS; (2) only reported region of interest (ROI) findings or small volume corrections in pre-selected ROIs; (3) data were already covered in one or more articles that were included in our analysis; (4) the patients had other uncontrolled diseases including liver or kidney or hematopoietic diseases, endocrine and immune diseases, mental disorders, malignancy, etc.; and (5) recruited participants were not adults. Studies of pulsatile tinnitus were also excluded owing to its unusual mechanism (Liu et al., 2018).

Authors of studies in which MNI or Talairach coordinates (necessary for voxel-level quantitative meta-analysis) were not explicitly reported were contacted to reduce the possibility of a biased sample set. In cases where the same or similar datasets were used in separate papers, only data from the analysis of the largest sample were included.

Recorded Variables

The following information was extracted from the selected studies: first author, year of publication, sample size, number of female participants, the mean age of participants, duration of tinnitus, type of MRI (1.5 or 3.0 T), image package, and full width at half maximum (FWHM). Statistically significant coordinates including the direction of GM volume or differential activity between tinnitus patients and HS were extracted. This information is shown in **Table 1**.

Quality Assessment

The quality of all included studies was assessed using an 11-point checklist that was based on those used in previous meta-analyses (Shepherd et al., 2012; Du et al., 2014). The checklist focused on both clinical and demographic characteristics of individual study populations as well as important scanner parameters and methodological details (**Table S1**) (Shepherd et al., 2012; Du et al., 2014).

Study selection and data extraction and summarization were independently performed in a standardized manner by two investigators (SC and GX); any disagreements were resolved by a third investigator (RS). This meta-analysis adhered to Preferred Reporting Items for Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). This meta-analysis has been registered with the PROSPERO International Prospective Register of Systematic Reviews of the University of York (PROSPERO registration no. CRD42019123399).

Standard Meta-Analyses of Structural and Functional Abnormalities

Abnormalities in brain structure and spontaneous activity were subjected to the voxel-wise meta-analysis by AES-SDM (https://www.sdmproject.com/software) (Radua et al., 2012a,b).

The extracted peak information was combined to recreate effect-size and variance maps first by means of a Gaussian kernel, which assigned higher effect sizes to voxels closer to the peaks. The FWHM was set at 20 mm in the assignment in order to control for false-positive results (Radua et al., 2012a). Taking sample size, intra-study variability, and between-study heterogeneity into account, study maps were calculated voxel-wise to obtain the random effects mean. Studies with larger sample sizes made a larger contribution because the mean map was weighted by the square root of the sample size of each study. Thresholds were applied using default settings (voxel threshold $P < 0.005$, peak height threshold $z > 1.00$, and cluster size threshold >10 voxels) after calculating for the meta-analysis means (Radua et al., 2012a). Finally, we statistically analyzed the meta-analysis effect-size map by comparing to a null distribution created with a permutation algorithm. A leave-one-out jackknife sensitivity analysis was used to test the reproducibility of VBM and ReHo study findings, which consisted of repeating the mean analysis after systematically removing each study.

In order to exclude potential heterogeneity resulting from different VBM measurement methods, we carried out a subgroup analysis of VBM studies including a scanner (1.5 or 3.0 T scanner) and FWHM (8 and 10 mm). Funnel plots of the peaks of the main findings were performed to check whether the findings might

TABLE 1 | Demographic and clinical characteristics of subjects in MRI datasets included in the meta-analysis.

Study	Analysis	Number (female)		Mean age (year)		Durations (month)	Hearing loss	MRI scanner	Software	Smoothing (FWHM)	P value	Correction method	Quality score
		TIN	HS	TIN	HS	TIN							
VBM STUDIES													
Mühlau et al. (2006)	VBM	28 (15)	28 (15)	40	39	53	No	1.5T	SPM2	8	<0.05	FDR	10
Landgrebe et al. (2009)	VBM	28 (13)	28 (13)	32.2	31.2	53.3	No	1.5T	SPM2	10	<0.05	FDR	10.5
Boyen et al. (2013)	VBM	31 (11)	24 (8)	56	58	12–348	Yes	3.0T	SPM5	8	<0.05	FWE	10
Melcher et al. (2013)	VBM	24 (12)	24 (12)	46.9	45.8	4.8–480	Mixed	3.0T	SPM8	8	<0.05	FWE	9.5
Krick et al. (2015)	VBM	22 (9)	22 (9)	42.6	NA	1.08	Mixed	3.0T	SPM8	10	<0.05	FWE	9.5
Allan et al. (2016)	VBM	73 (30)	55 (25)	58.38	56.91	NA	Mixed	1.5/3.0T	SPM8	10	<0.05	FWE	10.5
Schmidt et al. (2018)	VBM	15 (5)	15 (6)	55.13	52.93	>12	Mixed	3.0T	SPM12	10	<0.05	FWE	10
Han et al. (2018b)	VBM	21 (12)	21 (12)	44.1	43.5	20	No	3.0T	SPM8	8	<0.01	AlphaSim correction	10
ReHo STUDIES													
Jin et al. (2011)	ReHo	20 (12)	20 (13)	41	49.1	NA	Mixed	1.5T	SPM2	NA	<0.005	Uncorrected	8.5
Yang et al. (2014)	ReHo	18 (4)	20 (5)	43	42	16.8	Mixed	3.0T	SPM5	NA	<0.05	FWE	9.5
Chen et al. (2015)	ReHo	29 (13)	30 (15)	40.9	46.2	39.5	No	3.0T	SPM8	4	<0.01	AlphaSim correction	10.5
Cai et al. (2017)	ReHo	10 (6)	10 (6)	39.6	NA	NA	Mixed	3.0T	Dpabi	4	<0.001	TFCE	8.5
Han et al. (2018a)	ReHo	25 (15)	25 (15)	44.64	43.96	14	No	3.0T	SPM8	4	<0.001	AlphaSim correction	10.5
Han et al. (2018b)	ReHo	21 (12)	21 (12)	44.1	43.5	20	No	3.0T	SPM8	4	<0.05	AlphaSim correction	10
Fan (2018)	ReHo	7 (2)	14 (4)	40.86	48.50	>3	Mixed	3.0T	SPM8	6	<0.05	GRF	8.5

FDR, false discovery rate; FWE, family-wise error correction; FWHM, full width at half maximum; GRF, gaussian random field; HS, healthy subjects; MRI, magnetic resonance imaging; NA, not available; ReHo, regional homogeneity; SPM, statistics parameter mapping; T, tesla; TFCE, threshold-free cluster enhancement; TIN, patients with tinnitus; VBM, voxel-based morphometry.

have been driven by few or small studies. Meanwhile, the Egger test was also performed to detect the potential publication bias (Radua and Mataix-Cols, 2009).

Multimodal Analysis of the Structural and Functional Response

To identify brain areas exhibiting structural and functional alterations in tinnitus patients, the structural and functional data were cross validated in a single meta-analysis map by computing the union of structural and functional p values (Radua et al., 2012a).

Meta-Regression Analysis

To examine any potential effects, a meta-regression analysis weighted by sample size and intra- and between-study variances (Radua et al., 2012a) was performed to evaluate associations between changes in the brain and subject characteristics (age and duration of tinnitus). The probability threshold was decreased to 0.005 to minimize the detection of false associations. Findings for the slope and one of the extremes of the regressor were considered, and those in regions not detected in the main analysis were discarded. Finally, fits obviously driven by an insufficient number of studies were also discarded by inspecting the regression plot (Radua et al., 2012a).

RESULTS

Studies Included in the Meta-Analysis

The meta-analysis included 14 studies that met the inclusion criteria (**Figure 1**). There were eight VBM datasets with a total of 242 patients with tinnitus (107 females; mean age: 48.91 years) and 217 HS (100 females; mean age: 47.66 years), and seven ReHo studies with a total of 130 patients with tinnitus (64 females; mean age: 36.03 years) and 140 HS (70 females; mean age: 37.83 years). All of the patients in these studies were drug naïve and had not undergone a "washout" period prior to MRI scanning. The studies had a mean quality score of 9.73 out of a total possible score of 11, indicating that they were of high quality. There were no significant differences in age or sex ratio between the two groups. Details of the literature search and criteria for article inclusion are shown in **Figure 1**. The demographic characteristics, clinical variables, scanning method, and significance level of inter-group comparisons in the included studies are shown in **Table 1**.

Meta-Analyses of GM Volume Changes

Seven peak foci were reported in this VBM meta-analysis. Patients with tinnitus showed increased GM volume in the right STG ($P = 0.000$, $z = 1.084$), right MTG ($P = 0.000$, $z = 1.077$), left STG ($P = 0.000$, $z = 1.062$), and right angular gyrus ($P = 0.002$, $z = 1.024$), and a decreased volume in the right caudate nucleus ($P = 0.000$, $z = -1.472$), left SFG ($P = 0.000$, $z = -1.343$), and right supplementary motor are ($P = 0.001$, $z = -1.196$) relative to HS (**Figure 2A** and **Table 2**). The sensitivity analysis showed that all results above were highly reproducible, as most were preserved in combinations of the dataset (**Table S2A**).

Meta-Analyses of ReHo Abnormalities

A total of four peak foci were reported in the ReHo studies. AES-SDM of the fMRI data revealed hyperactivation in the right MTG ($P = 0.000$, $z = 1.775$), right middle occipital gyrus ($P = 0.002$, $z = 1.422$), left precuneus ($P = 0.002$, $z = 1.460$), and right inferior parietal (excluding supramarginal and angular) gyri ($P = 0.003$, $z = 1.406$) of tinnitus patients relative to HS (**Figure 2B** and **Table 3**). The jackknife sensitivity analyses showed that these results were highly reproducible (**Table S2B**).

Multimodal Analysis of GM Volume and Brain Response

We summarized our findings into a single meta-analytic map in order to identify regions showing abnormalities in both VBM and ReHo studies. The multimodal analysis revealed significant differences in the right MTG ($P < 0.0025$) of patients with tinnitus relative to HS.

Heterogeneity Analysis and Publication Bias

The heterogeneity analysis indicated significant heterogeneity among the VBM studies with altered GM volume in the right STG, right MTG, and left STG ($P < 0.005$) (**Table S3**) and showed insignificant heterogeneity among the ReHo studies. We conducted the funnel plots and Egger tests, although there were too few VBM and ReHo studies for evaluation of publication bias in the meta-analysis, which requires at least 10 studies. The funnel plots demonstrated that the main findings were driven by at least seven VBM studies and six ReHo studies, respectively (**Figure S1**). Analysis of publication bias revealed that the Egger tests were insignificant in the peaks of the altered brain regions in the VBM meta-analysis ($P = 0.715$) and the ReHo meta-analysis ($P = 0.990$).

Subgroup Analysis

A subgroup analysis of VBM studies using different FWHM values (8 mm/10 mm) yielded no significant differences. The subgroup analysis of VBM studies using different scanners (1.5/3.0 T) revealed structural abnormality in the left medial SFG and right supplementary motor area of patients with tinnitus (**Table S4**).

Meta-Regression

Although it is not recommended for fewer than nine studies (Radua and Mataix-Cols, 2009), we carried out a meta-regression analysis to examine potential confounding variables (mean age and disease duration). The mean age of patients was associated with increased GM volume in the bilateral STG, right MTG, right angular gyrus in VBM studies (**Table S5A**). Moreover, the mean age of patients was associated with hyperactivation in the right MTG and right middle occipital gyrus in ReHo studies (**Table S5B**). The meta-regression of disease duration showed insignificance among the brain regions in VBM studies and ReHo studies.

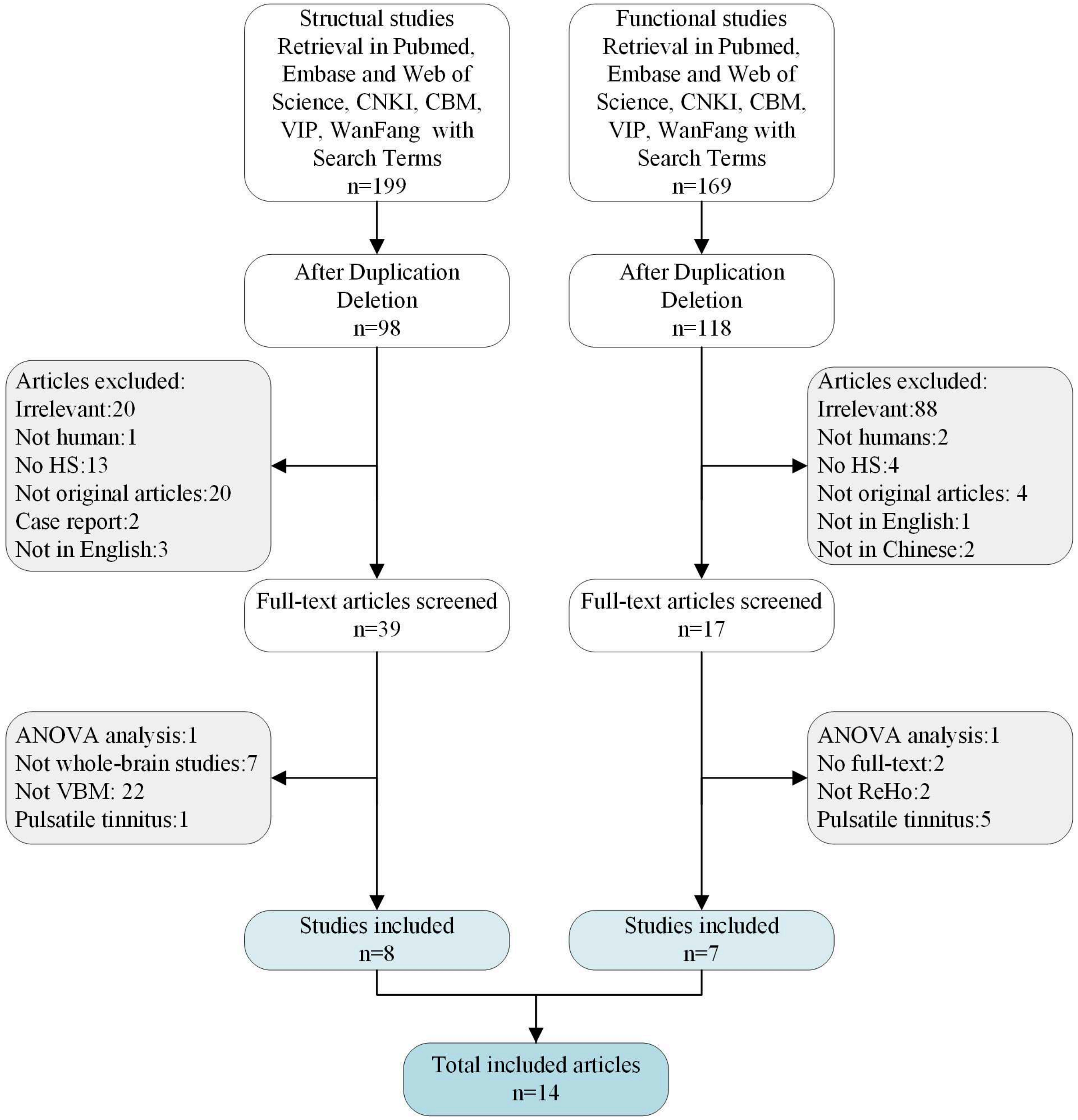

FIGURE 1 | The flow diagram for studies included in the present meta-analysis.

DISCUSSION

This is the first multimodal neuroimaging meta-analysis investigating the neural substrates of tinnitus by combining information from whole-brain VBM studies of GM volume and ReHo studies of spontaneous brain activity.

The main findings were that GM volume was increased in bilateral STG, the right MTG, and right angular gyrus and decreased in the right caudate nucleus, left medial SFG, and right supplementary motor area of patients with tinnitus compared with HS (**Figure 2A** and **Table 2**). Additionally, tinnitus was associated with hyperactivation in the right MTG, right middle occipital gyrus, left precuneus, and right inferior parietal (excluding supramarginal and angular) gyri (**Figure 2B** and **Table 3**). These results remained unchanged when each study was removed in the jackknife sensitivity analysis.

Abnormalities are more frequently reported in the STG and MTG than in other parts of the auditory cortex in neuroimaging studies of tinnitus (Boyen et al., 2013; Chen et al., 2014; Han et al., 2018a). The temporal gyrus is critical for auditory

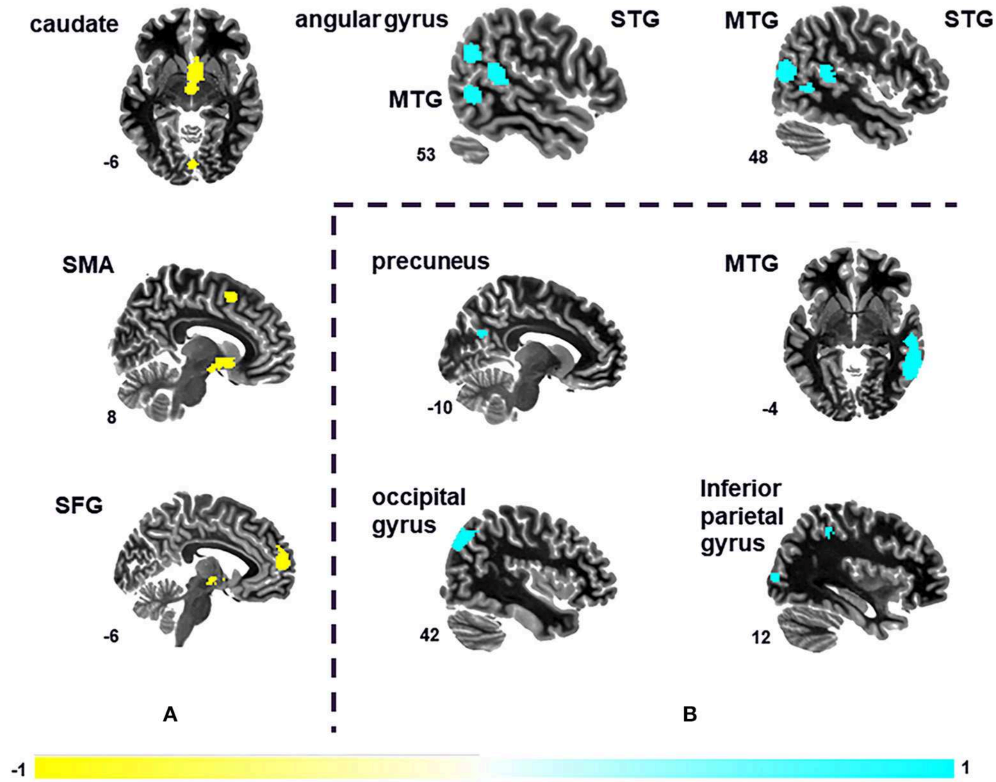

FIGURE 2 | Differences in the brain regions between tinnitus patients and HS. **(A)** Differences in gray matter (GM) volume between tinnitus patients and HS. **(B)** Changes in spontaneous brain activity of tinnitus patients compared with HS. MTG, middle temporal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus.

processing that includes simple auditory stimulus processing and semantic memory (May and Tiitinen, 2010; Recasens et al., 2014), and is a connection in the hierarchical structure of the primary auditory cortex and frontal lobe (Ishishita et al., 2019). Our results revealed abnormal brain responses in this region, suggesting their involvement in tinnitus. Prolonged exposure to an internal sound such as a tone and/or noise is associated with increased GM volume in cortical regions of auditory processing (Boyen et al., 2013).

Tinnitus patients often exhibit varying degrees of hearing impairment. Hearing loss patients with or without tinnitus use more contextual information from semantic memory to maintain normal communication, which may result in increased GM volume of the auditory association area (Boyen et al., 2013). However, a recent neuroimaging study did not find any differences in the temporal gyrus between recent-onset patients with tinnitus with mild hearing impairment and HS (Krick et al., 2015). As the present meta-analysis included patients with tinnitus as well as those without hearing loss, we were unable to perform a regression analysis of hearing loss severity. In addition, differences in the temporal gyrus have been reported between long-term and recent-onset patients with tinnitus (Schmidt et al., 2018). Although this implies that the duration of tinnitus alters the temporal gyrus, we did not find any correlation between these two variables in this meta-analysis. Furthermore, some studies have shown increased neuronal activity in the right hemisphere—especially the right MTG—in tinnitus (Mirz et al., 1999; Chen et al., 2014), whereas others have reported left lateralization (Langguth et al., 2006; Geven et al., 2014). Therefore, although the right MTG involvement found in this study suggests right lateralization, most patients exhibited unilateral or bilateral tinnitus, making it difficult to conclude that tinnitus has a unilateral tendency.

Tinnitus sensation representations generated or expressed in auditory cortex are necessary (Lanting et al., 2009) but not sufficient to account for suffering from tinnitus. Central auditory system hypotheses of tinnitus genesis have been proposed to account for the discrepancy between audiometric profile and tinnitus perceptual attributes, including thalamocortical dysrhythmia in frequencies (Llinas et al., 1999; Weisz et al., 2007), the striatal gating model (Larson and Cheung, 2012), etc. Decreased GM volume of caudate nucleus has been found in patients with tinnitus in this meta-analysis, supporting that the striatal gating model might be involved in tinnitus genesis. The caudate nucleus has been found be projected from the superior temporal cortex and rostral and midportion aspects of association cortex on the superior temporal gyrus in monkeys and cats (Reale and Imig, 1983; Yeterian and Pandya, 1998). This nucleus is hypothesized to act as a gating mechanism for auditory phantom percepts, which can suppress the enduring

TABLE 2 | VBM brain regions showing GM differences between tinnitus patients and healthy subjects.

	MNI coordinates			SDM z-score[a]	P value[b]	Number of voxels[c]	Cluster breakdown (number of voxels)	Heterogeneity	Sensitivity
	x	y	z						
TIN > HS									
R superior temporal gyrus	50	−40	12	1.084	0.000	254	R superior temporal gyrus, BA22, BA41, BA42 (138)	Yes	7/8
							R arcuate network, posterior segment (64)		
							R superior temporal gyrus, BA21, BA42 (20)		
							Corpus callosum (11)		
R middle temporal gyrus	48	−70	12	1.077	0.000	224	R middle temporal gyrus, BA37, BA39 (163)	Yes	7/8
							R middle occipital gyrus, BA19, BA39 (45)		
L superior temporal gyrus	−46	−34	10	1.062	0.000	203	L superior temporal gyrus, BA41., BA48 (84)	Yes	6/8
							L arcuate network, posterior segment (53)		
							Corpus callosum (32)		
							L Rolandic operculum, BA48 (10)		
R angular gyrus	56	−58	28	1.024	0.002	106	R angular gyrus, BA22, BA39, BA40 (95)	No	6/8
TIN < HS									
R caudate nucleus	4	8	−6	−1.472	0.000	599	R striatum (119)	No	6/8
							R olfactory cortex, BA25 (41)		
							R anterior thalamic projections (35)		
							L anterior thalamic projections (30)		
							L olfactory cortex, BA25 (23)		
							Anterior commissure (21)		
							R caudate nucleus, BA25 (14)		
							L caudate nucleus, BA25 (12)		
							Corpus callosum (10)		
L superior frontal gyrus, medial	−8	56	12	−1.343	0.000	358	L superior frontal gyrus, BA10 (261)	No	7/8
							Corpus callosum (80)		
R supplementary motor area	8	10	54	−1.196	0.001	106	Corpus callosum (51)	No	6/8
							R supplementary motor area, BA6 (48)		

[a] *Peak height threshold: $z > 1$.*
[b] *Voxel probability threshold: $P < 0.005$.*
[c] *Cluster extent threshold: regions with <10 voxels are not reported in the cluster breakdown.*
BA, Brodmann area; GM, gray matter; HS, healthy subjects; L, left; MNI, Montreal Neurological Institute; R, right; SDM, signed differential mapping; TIN, tinnitus patients; VBM, voxel-based morphometry.

tinnitus loudness (Larson and Cheung, 2013). The requisite cortico-striatal neural circuitry is in place for dysfunction striatal connectivity to enable perception of auditory phantoms (Larson and Cheung, 2012; Hinkley et al., 2015).

We also found decreased GM volume of SFG in patients with tinnitus. This brain region plays an important role in executive function and emotion processing and attention, in contrast to the sensory processing that is affected in chronic tinnitus (Mirz et al., 2000; Weisz et al., 2004). Results from resting-state fMRI studies indicate that SFG is the main cortical area affected by tinnitus (Chen et al., 2014, 2016). Moreover, disrupted functional connectivity between the SFG and amygdala has been observed in patients, suggesting that executive control of attention network in the SFG enhances the negative attributes of tinnitus contributed by the amygdala (Chen et al., 2017). A decreased SFG GM volume has been attributed to peripheral hearing loss (Husain et al., 2011; Boyen et al., 2013). In our meta-analysis, there was no available uniform audiometric data reported in the included studies, making it difficult to distinguish between the effects of hearing impairment and tinnitus on SFG alteration.

Besides auditory brain regions, auditory spatial information is also processed by the visual centers of the brain (Bedny et al., 2010; Fiehler and Rosler, 2010). Increased activity in the right middle occipital gyrus of patients with tinnitus were observed in the current meta-analysis. This brain region participates in visual processing, which may be processed cross-modally in phantom auditory perception (Murray et al., 2005). Furthermore, the increased GM volume of angular and hyperactivation of precuneus were revealed in this meta-analysis. Interestingly, the MTG, angular gyrus, and precuneus also belong to the default mode network (DMN), which is most active at rest (Raichle et al., 2001; Mantini et al., 2007). These aberrant neural activities may be responsible for the dysfunction of DMN in patients with tinnitus, although the source or their type within specific DMN regions due to tinnitus remains unclear.

TABLE 3 | Brain regions showing spontaneous brain activity differences between patients with tinnitus and healthy subjects.

	MNI coordinates			SDM z-score[a]	P-value[b]	Number of voxels[c]	Cluster breakdown (number of voxels)	Heterogeneity	Sensitivity
	x	*y*	*z*						
TIN > HS									
R middle temporal gyrus	60	−44	−4	1.775	0.000	442	R middle temporal gyrus, BA21, BA22, BA37 (374)	No	6/7
							R arcuate network, posterior segment (30)		
R middle occipital gyrus	34	−92	6	1.422	0.002	134	R middle occipital gyrus, BA18 (102)	No	4/7
							R inferior network, inferior longitudinal fasciculus (19)		
L precuneus	−10	−64	28	1.460	0.002	127	L median network, cingulum (69)	No	5/7
							L precuneus, BA23 (32)		
							L cuneus cortex (14)		
R inferior parietal (excluding supramarginal and angular) gyri	34	−44	46	1.406	0.003	38	R inferior parietal (excluding supramarginal and angular) gyri, BA40 (17)	No	5/7

[a] *Peak height threshold: $z > 1$.*
[b] *Voxel probability threshold: $P < 0.005$.*
[c] *Cluster extent threshold: regions with <10 voxels are not reported in the cluster breakdown.*
BA, Brodmann area; HS, healthy subjects; L, left; MNI, Montreal Neurological Institute; R, right; SDM, signed differential mapping; TIN, patients with tinnitus.

The analysis of heterogeneity showed that findings from structural neuroimaging studies were inconsistent, while the subgroup analysis using a different scanner revealed different structural abnormalities in the left medial SFG and right supplementary motor area among patients with tinnitus. In addition, the mean age of patients was associated with increased GM volume in the bilateral STG, right MTG in VBM studies. This variability could be due to small sample sizes, demographic characteristics, and methodological differences (e.g., in the scanner) among studies. One study reported differences in GM of various brain regions between patients with mild and more severe long-term tinnitus (Schmidt et al., 2018). We did not perform meta-regression of tinnitus severity in this study as the different questionnaires used to assess tinnitus symptoms were not uniform; however, the severity of tinnitus may also contribute to the observed heterogeneity.

The multimodal analysis revealed significant differences in the right MTG of patients with tinnitus and HS. The temporal cortex—specifically the MTG—was found to be altered in patients with tinnitus (Mirz et al., 1999; May and Tiitinen, 2010; Chen et al., 2014; Recasens et al., 2014), suggesting that this brain area is closely associated with tinnitus development (Farhadi et al., 2010).

The present study had some limitations. First, a relatively limited number of datasets were analyzed owing to the exclusion criteria. There were only 14 studies included totally; the results of this meta-analyses were preliminary. Second, patients with tinnitus, both with and without hearing loss, were included, which precluded a regression analysis of hearing loss severity.

In conclusion, the results of our meta-analysis revealed abnormalities not only in auditory areas but also in the caudate nucleus, which suggests the involvement of the cortico-striatal circuits in the neuropathology of tinnitus.

DATA AVAILABILITY STATEMENT

The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

RS, SC, and FL contributed to study conception and design and conceived the data analysis strategy. SC, GX, and JZ acquired the data. SC, GX, and RS collated and analyzed the data. SC, GX, and JZ drafted the manuscript. YQ, ZL, ZH, TY, PM, RS, and FL discussed, read, and revised the manuscript. All authors approved the publication of this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.00028/full#supplementary-material

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SYSTEMATIC REVIEW
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Explicit and Implicit Own's Body and Space Perception in Painful Musculoskeletal Disorders and Rheumatic Diseases: A Systematic Scoping Review

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Background: Pain and body perception are essentially two subjective mutually influencing experiences. However, in the field of musculoskeletal disorders and rheumatic diseases we lack of a comprehensive knowledge about the relationship between body perception dysfunctions and pain or disability. We systematically mapped the literature published about the topics of: (a) somatoperception; (b) body ownership; and (c) perception of space, analysing the relationship with pain and disability. The results were organized around the two main topics of the assessment and treatment of perceptual dysfunctions.

Methods: This scoping review followed the six-stage methodology suggested by Arksey and O'Malley. Ten electronic databases and grey literature were systematically searched. The PRISMA Extension for Scoping Reviews was used for reporting results. Two reviewers with different background, independently performed study screening and selection, and one author performed data extraction, that was checked by a second reviewer.

Results: Thirty-seven studies fulfilled the eligibility criteria. The majority of studies (68%) concerned the assessment methodology, and the remaining 32% investigated the effects of therapeutic interventions. Research designs, methodologies adopted, and settings varied considerably across studies. Evidence of distorted body experience were found mainly for explicit somatoperception, especially in studies adopting self-administered questionnaire and subjective measures, highlighting in some cases the presence of sub-groups with different perceptual features. Almost half of the intervention studies (42%) provided therapeutic approaches combining more than one perceptual task, or sensory-motor tasks together with perceptual strategies, thus it was difficult to estimate the relative effectiveness of each single therapeutic component.

Conclusions: To our knowledge, this is the first attempt to systematically map and summarize this research area in the field of musculoskeletal disorders and rheumatic diseases. Although methodological limitations limit the validity of the evidence obtained, some strategies of assessment tested and therapeutic strategies proposed represent useful starting points for future research. This review highlights preliminary evidence, strengths, and limitations of the literature published about the research questions, identifying key points that remain opened to be addressed, and make suggestions for future research studies. Body representation, as well as pain perception and treatment, can be better understood if an enlarged perspective including body and space perception is considered.

Keywords: musculoskeletal disorders, rheumatic diseases, chronic pain, somatoperception, body perception, body representation, body ownership, scoping review

INTRODUCTION

The body is a unique multisensory object (Longo et al., 2008a) integrating a large variety of inputs both from the outside and from within the body (Gallace and Spence, 2008), thus offering the opportunity for a better interaction with the complex surrounding world (Medina and Coslett, 2016a). We can experience our own body through the basic somatic sensations of touch, warmth, cold, proprioception, nociception and itch coming from peripheral receptors to central specific cortical areas (*somatosensation).* However, our body interaction with the surrounding world is also made by more rich and complex experiences, as the estimation of body size and shape, or the perception of body parts localization in external space *(somatoperception)* (Taylor-Clarke et al., 2004; Longo and Haggard, 2010) for which there are no specialized sensory receptors. The achievement of this more sophisticated perceptual experience requires moving beyond pure *somatosensation* to a higher-order level of neural machinery in which a combination of somatic information converges in associative areas (Murata and Ishida, 2007; Murata et al., 2016) to produce a multimodal representation of the body as a whole (the so called body matrix) (Moseley et al., 2012). This "on line" organization of somatic information is checked for congruence against internal body models (*somatorepresentations)* (Schwoebel and Coslett, 2005; de Vignemont, 2007; Carruthers, 2008; Tsakiris and Fotopoulou, 2008; Berlucchi and Aglioti, 2010; Longo, 2015; Medina and Coslett, 2016a): if the "on line" representation does not match (Azañón and Haggard, 2009) the "off line" body memory (Riva, 2018) we experience a body incoherence, from which misperceptions and bodily illusions may arise.

Abbreviations: 2-PET, 2-Point Estimation Task; BO, Body Ownership; BID, Body Image Drawing; CLBP, Chronic Low Back Pain; CNP, Chronic Neck Pain; CRAF, Computerized Rod And Frame test; CRPS, Complex Regional Pain Syndrome; FreBAQ, Fremantle Back Awareness Questionnaire; FreKAQ, Fremantle Knee Awareness Questionnaire; MDRDs, Musculoskeletal Disorders and Rheumatic Diseases; MNss, Motor-Neglect sub-scale; NLSQ, Neglect-Like Symptoms Questionnaire; PTP, Point-to-Point; RHI, Rubber Hand Illusion; SoP, Somatoperception; SpP, Space Perception; SVV, Subjective Visual Verticality; SVH, Subjective Visual Horizontality; WAD, Whiplash Associated Disorders.

In addition, as a part of our body interaction with the surrounding world, how we experience our own's body relates also to our sense of self, understood as the perceptual feeling that a body part belong to us (*ownership*), and is under our own control (*agency*) (Tsakiris et al., 2006; Longo et al., 2008a). Internal mental representation of the body includes the shape and contours of own body, the perceived location of body parts, and the boundaries between them and external objects. Body ownership and body agency can be tested experimentally through the Rubber Hand Illusion (RHI) paradigm (Botvinick and Cohen, 1998), in which tactile stimuli are applied synchronously over a prosthetic hand placed in front of the participant, and on his actual hand hidden from view. This produces an illusory sense of incorporation of the rubber hand as it was the participant's own hand (Botvinick, 2004). Overall, how we experience our body and space around us results from the integration of at least three different sub-functions: (a) the perception we have of our own body (*somatoperception—SoP*); (b) the perception of the space around us in which we are immersed (space perception—SpP); and (c) the integration of the two body experiences in order to produce a coherent sense of self (*body ownership—BO*). Up to now we have only a partial knowledge of the operational mechanisms guiding *SoP* because a large number of studies conducted in the fields of experimental psychology and neurophysiology have mainly studied the basic mechanisms of *somatosensations* while we know much less about the higher-order mechanisms involved in SoP (Longo et al., 2010). Moreover, the research lines have increased the interest on *BO* and SpP only in the last one or two decades (Ramakonar et al., 2011; Trojan et al., 2014).

Musculoskeletal Disorders and Rheumatic Diseases (MDRDs) are a group of diseases commonly affecting bones, muscles and joints (van der Heijde et al., 2018) that often cause chronic pain with a severe impact on the quality of life of patients (March et al., 2014; Blyth et al., 2019), loss of work productivity (Daneshmandi et al., 2017), and significant economic costs for the community (Bevan, 2015; Vos et al., 2017; Briggs et al., 2018). Notably, pain and body perception are essentially two subjective mutually influencing perceptual experiences (Haggard et al., 2013; Trojan et al., 2014): the fast and accurate perception of pain is essential to protect the body, and the perception of body integrity is needed to avoid pain (Wand et al., 2016). Thus, the study of errors in processing the *explicit* (conscious) and *implicit* (unconscious) body experience, as in the case of illusion phenomena (Medina and Coslett, 2016b), may represent a useful opportunity to understand how the brain constructs functional representations of the body in patients with MDRDs, and on pain perception itself (Pamment and Aspell, 2017; Fang et al., 2019) in these clinical conditions. However, existing studies on *SoP*, SpP, and *BO* were largely conducted on healthy subjects (Longo et al., 2008a; Fuentes et al., 2013; Longo, 2017), and clinical research has mostly investigated neurological conditions (Haggard and Wolpert, 2005; Pia et al., 2013, 2016), eating disorders (Keizer et al., 2011; Scarpina et al., 2014; Spitoni et al., 2015; Gadsby, 2017), and neuropathic pain syndromes such as Complex Regional Pain Syndrome-CRPS (Galer and Jensen, 1999; Förderreuther et al., 2004; Lewis et al., 2007; Reinersmann et al., 2013). A large body of literature on the field of MDRDs has instead investigated primary somatosensations (Tsay et al., 2015), mainly tactile acuity (Catley et al., 2013, 2014; Harvie et al., 2018) and proprioceptive precision (Stanton et al., 2016; Tong et al., 2017; Lin et al., 2019), referring generically to disturbances at the level of perception or mental representations. However, both two-point discrimination and joint repositioning error (two of the most frequently investigated tasks) cannot be considered as having a higher-order somatoperceptual involvement (Longo and Haggard, 2010; Hillier et al., 2015; Spitoni et al., 2015). The area of MDRDs thus lacks a comprehensive knowledge about the more complex implicit and explicit body and space perception.

Evidence supporting the interaction between pain and the three mentioned domains of body experience (SoP, SpP, BO) have been found in experimentally-induced pain (Moseley et al., 2008; Gallace et al., 2011; Mancini et al., 2011; Fang et al., 2019) (e.g., distorting the visual appearance of the body). Moreover, a correlation between body and space perception dysfunctions with pain intensity and its duration (Förderreuther et al., 2004; Peltz et al., 2011; Reinersmann et al., 2012), were found in CRPS, thus it would be clinically relevant to clarify if this interaction exists also in MDRDs.

In order to have a comprehensive and structured knowledge of how body experience has been investigated in MDRDs, we systematically reviewed the literature published about the implicit and explicit mechanisms of: (a) *somatoperception* (and indirectly on *somatorepresentations*); (b) *body ownership*; and (c) *space perception*.

The primary goal of this study was to map and examine the quantity and the nature of the scientific literature concerning the implicit and explicit own's body and space perception, organizing the findings around three main topics:

a) the adopted strategies of assessment for perceptual dysfunctions;
b) the impact of perceptual disorders in MDRDs compared to other disorders (e.g., CRPS) and in sub-groups of MDRDs;
c) the interventions proposed to approach perceptual disorders associated to MDRDs.

MATERIALS AND METHODS

The scoping methodology has been adopted because represents the most appropriate method to overview the literature about an emergent research area that is still fragmented, complex, wide, poorly understood or not deeply investigated before (Colquhoun et al., 2014, 2017). The review followed the PRISMA Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018). A detailed PRISMA-ScR is provided **Additional File 1**. Every deviation from the published protocol (Viceconti et al., 2018) or added procedure were declared. Neuroscientists (ML, AG, MP) and physiotherapists (AV, DL, DP, DR, GR, MT) constituted an inter-professional and interdisciplinary research team with both clinical and scientific background to better approach, from a rehabilitative perspective, a research area that has been historically treated by neuropsychological disciplines (Head and Holmes, 1911; Haggard and Wolpert, 2005; Medina and Coslett, 2016b). In agreement with the concept of a "literature map," the results are graphically presented in **Figures 3–8**.

Eligibility Criteria

Inclusion and exclusion criteria are reported in **Table 2**. An iterative process, rather than a fixed and pre-established searching schema, is one of the features characterizing scoping reviews: eligibility criteria were updated in progress by an iterative process based on feedback provided by authors, in order to better refine the searching process according to the research questions (see the step 1 of the **Figure 1**).

We adopted *a priori* operational definitions of the key terms used (see **Table 1** for terminological aspects) in order to avoid terminological misunderstanding. Themes like those dealing with *somatosensation*, *somatosensory representation*, body scheme, body structural description, body concept, and body affect were not considered as the main focus of this review. In particular, s*ensory representations* and *somatosensations* were often used in literature as a surrogate for *perceptual representations* and *somatoperception,* mainly to describe their associated dysfunctions. Readers are invited to see Flor et al. (1997), Flor (2003), and Hotz-Boendermaker et al. (2016) for maladaptive reorganizations of *somatosensory representations*, and Tsay et al. (2015) for a comprehensive review on *somatosensations*. Moreover, we have deliberately avoided the use of the umbrella term "body image" given the controversies and interpretational difficulties with this term (de Vignemont, 2010; Pitron et al., 2018; Gadsby, 2019): it has often been used as a "*passepartout*" term, lumping together phenomena and psychological capacities quite different from each other, often referred to beliefs and affective attitudes related to the body (Mohr et al., 2010). We have to consider that words used in literature to describe body perception, mental representations and the relative assigned meanings are sometimes ambiguous or contradictory (Gallagher, 1986) and often depend on the observer's professional background., Thus, to better organize the results emerged from the review we have referred to the theoretical model proposed by Longo et al. (2010), Longo (2016) and adapted it for the purposes of this study.

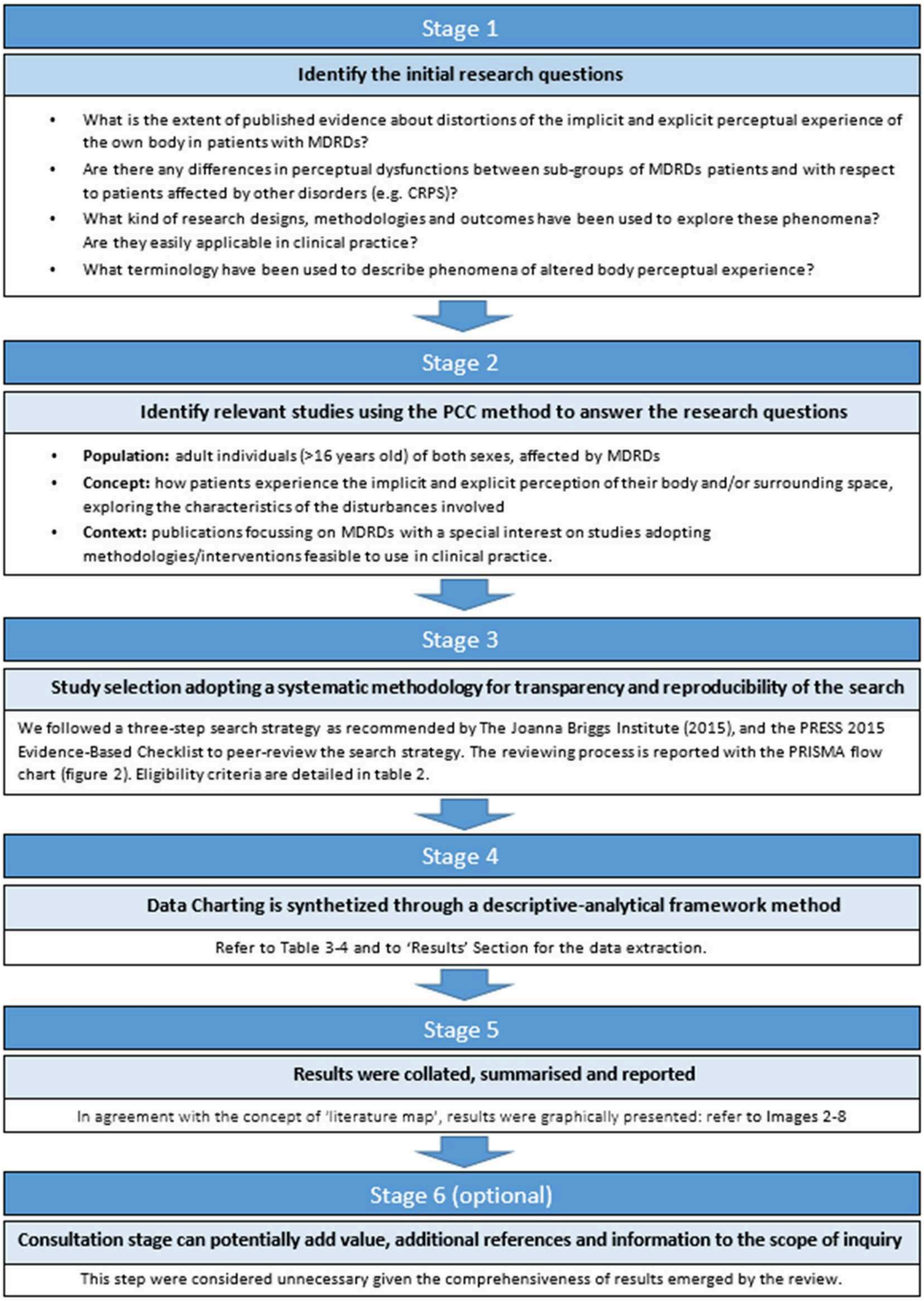


FIGURE 1 | Summary of the adopted guidance framework for scoping reviews.

Searching Strategy and Information Sources

In line with the published protocol, we followed a three-step search strategy as recommended by The Joanna Briggs Institute (2015). A preliminary search strategy was developed, pilot-tested and peer-reviewed by two authors with different background (a physiotherapist expert in research methodology—DR, and a neuropsychologist—AG), by using the PRESS 2015

TABLE 1 | Terminological definitions.

Mechanisms	Meanings	Tasks (examples)	Neural bases
Somatosensations	*"How owns body is felt to be like?"* They are the basics mechanisms producing the sensations of touch, proprioception, cold, warm, nociception, vision, etc., for which we own specific receptors, encoding the input information according to the particular type of stimulus processed.	Tactile stimuli detection, precision of touch (e.g., two-point discrimination threshold), repositioning accuracy (e.g., joint position sense).	***Sensorial Representations:*** Primary Somatosensory cortices.
Somatoperceptions	*"How owns body is perceived to be like?"* It is referred to the complex perceptual tasks, for which we not own specialized receptors.	Perception of body parts' size and location, the skin localization of tactile stimuli, tactile object recognition, spatial localisation of touch.	***Perceptual representations:*** Superficial schema, postural schema and body model. Parietal cortices, especially in right hemisphere.
Somatorepresentations • *Somatosensory Representation* • *Perceptual Representation* • *Cognitive Representation*	With this "umbrella term" it can be grouped a variety of functional and neural configurations about different body characteristics (e.g., sensorial, perceptual or cognitive). In this sense, the conceptual term *"representation"* can assume a variety of meanings on the base of what features are specifically analysed.		
Cognition	*"How owns body is believed, remembered to be like?"* It is referred to a cognitive reflection about the body.	Body structural description, general semantic knowledge, formation of attitudes and emotion toward the body.	***Cognitive Representations:*** *E*specially in left hemisphere.

Adapted and modified from Longo et al. (2010). Substantial differences exist between the two high-order processes represented by the somatoperception and somatorepresentation, from the basics mechanisms of the somatosensations (Longo et al., 2010). Despite these three different mechanisms are integrated and linked (Moseley et al., 2012), they may be dissociable, at least partially, because each one is based on different functional and neuroanatomical underlying structures and mechanisms: see Longo et al. (2010) for a review on the neural bases of body representations and Medina and Coslett (2016b) for descriptions of clinical cases highlighting this dissociation.

Evidence-Based Checklist (McGowan et al., 2016). Modifications to the search string were made after reviewers' suggestions. Searching history and the peer-reviews of the search strategy are available under request. In addition to the procedure described in the protocol, the "Similar Articles" function of PubMed was used and the snowball technique adopted when additional articles were found (Greenhalgh and Peacock, 2005).

Electronic Databases

Electronic search was conducted by one author (AV) between May 2018 until September 2018 on 10 electronic databases and grey literature (a full description is provided in the **Additional File 2**). Very broad search terms were employed for a more sensitive rather than specific search of the literature aimed at meeting the primary goal of the scoping review to systematically map the literature. A secondary review was made by scanning the Gray Matters Checklist.[1]

Study Selection

Two reviewers with different background independently evaluated records for eligibility of title/abstract (DL and EC) and full texts screening (AV and MP). Any disagreement was resolved by discussion between reviewers or, in case of persistent disagreement, a third reviewer (MT) was introduced to reach a consensus. The reviewing process is detailed on the PRISMA flow chart (**Figure 2**).

[1]https://www.cadth.ca/resources/finding-evidence/grey-matters

Calibration Phase

Both for the screening of titles/abstracts and for the selection of full-texts the raters performed a series of pilot tests as a calibration exercise to improve the reliability of judgments and agreement between evaluators (Tricco et al., 2018). Each round of pilot testing was accompanied by explanatory documents in which eligibility criteria were updated and clarified, and specification about potentially conflicting terminology were provided in order to avoid interpretation errors. For all pre-formal screening test, inter-rater percentage agreement had to be >90% before starting the formal screening (Colquhoun et al., 2017) (further information are provided in the published protocol). Feedback from evaluators were used to refine the inclusion/exclusion criteria (see the difference between **Table 2** in the present study and its counterpart in the published protocol).

Data Analysis

Findings emerged from the retrieved studies were organized around the research questions. Due to the heterogeneity of studies, in terms of research designs, methodological issues and clinical conditions investigated, we adopted a qualitative-descriptive synthesis, as suggested by the PRISMA-ScR (Tricco et al., 2018), and following the approach recommended by the Cochrane Group (Higgins and Green, 2008) and the (Centre for Reviews Dissemination, 2009). In case of incomplete or missing data, the authors of the included papers were contacted for further information. Data were extracted by a single reviewer (AV) using a standardized Excel spreadsheet designed for this study and adapted after the pilot trial charting exercise.

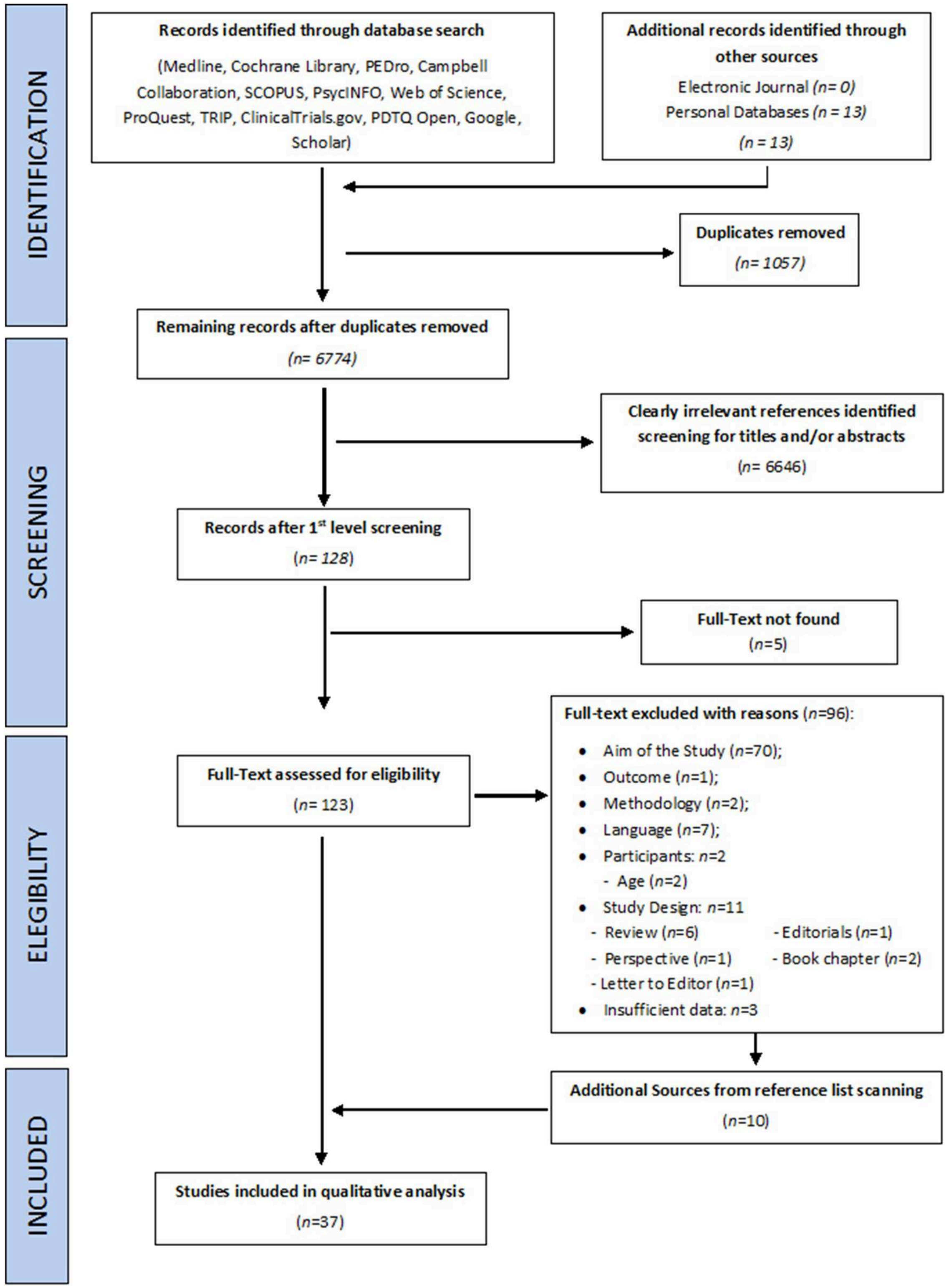


FIGURE 2 | PRISMA flow diagram detailing the selection of sources of evidence.

TABLE 2 | Eligibility criteria for inclusion and exclusion studies.

Inclusion criteria	Exclusion criteria
Aim: studies investigating alterations of the implicit/explicit body perception or perceptual dysfunctions of peri-/extra- personal space. Studies investigating the body ownership (e.g., the rubber hand illusion phenomena). Intervention studies on specific form of perceptual training (e.g., localization sensory training) or involving the perceptual manipulation of body parts as the main content of the therapy (>50%). Intervention studies not adopting perceptual rehabilitation or perceptual manipulations were included only if they considered the effectiveness of proposed interventions with respect to objectively or subjectively measured body perception dysfunctions, as a primary or secondary outcome. **Language:** full text in English Language[a]. **Setting:** experimental or clinical[b]. **Participants:** • Studies on humans (>16 y old), male and female. • Patients affected by musculoskeletal disorders or rheumatic diseases (e.g., LBP, neck pain, osteoarthritis, rheumatoid arthritis, fibromyalgia, etc.), including radicular syndromes (radicular pain and radiculopathies). **Study Design:** • Primary research studies: ○ Quantitative design (including proceedings[c], conference abstracts[c]): - Experimental designs (RCT, controlled clinical trials); - Observational designs (descriptive studies, surveys, cohort studies, cross-sectional studies, observer-reported or patient-reported outcome studies, case studies[d]/series[d], proceedings[d]; ○ Qualitative designs: all types of qualitative research designs. • Secondary research studies[e]: systematic review with or without meta-analysis, meta-summary, meta-synthesis. **Outcomes:** • Quantitative research designs: ○ Primary Outcomes: - measures, methodologies and tests assessing implicit/explicit body perception dysfunctions and/or alterations of surrounding space perception; self-reported pain, neurophysiologic threshold measures of pain (e.g., electrical pain threshold or pain pressure threshold); - the association between pain (intensity and duration) and disturbances of the implicit/explicit body perception, space perception and body ownership. ○ Secondary Outcomes: - self-reported disability and measures of physical functionality; - the association between neuro-anatomical and/or neurophysiologic correlates and measures of body perception. • Qualitative research designs: ○ Primary Outcomes: - Interpretation of body image drawings; - the frequency and typology of words used by patients in describing the alterations of own implicit and explicit body experience. Themes and subthemes will be derived by the analysis of patients' interview.	**Aim:** studies investigating body perception in relation to action, both in congruent and incongruent conditions (e.g., the illusion of virtual walking, the mirror therapy, the ability to imagine movements of body parts or to mentally rotate body parts as in the case of motor imagery, the left/right discrimination tasks, or the video-interpretation of own's body in dynamic conditions). Studies investigating the body/self-image with the meaning of the satisfaction about own bodily appearance, physical efficacy and general health, or concerning the body esteem, and self-acceptance. Studies investigating the concept of the body awareness or interoception referred as the general a-specific ability to notice subtle internal bodily sensations/states and emotions, or referred to the generic concept of the "mind-body" connection. Studies using body awareness-oriented intervention (e.g., breath relaxation, concentration, body scan) or belong to the broad umbrella of Body Awareness Interventions (BAI). Studies investigating the balance or posturography, tactile acuity (two-point discrimination threshold), joint repositioning error (or repositioning accuracy), sensorimotor mismatch and sensory/sensorimotor training with tasks involving aspects of somatosensation (e.g., tactile acuity training or JPS training). **Language:** full text and abstract not in English Language[f]. **Participants:** • Patients affected by: - neuropathic pain (e.g., Complex Regional Pain Syndrome—CRPS, Phantom Limb Pain) or myelopathies; - eating disorders (e.g., anorexia, bulimia); - psychiatric or neurological conditions (e.g., personality dissociation, somatoform disorders, Body Identity Integrity Disorders – BIID, dementia, Alzheimer and Parkinson diseases, Multiple Sclerosis, Stroke, Cerebral Palsy, Spinal Cord Diseases); - congenital, hereditary or endocrine abnormalities and deformities (e.g., pectus carinatum, phocomelia, acromegaly, gigantism, Marfan Syndrome, benign joint hypermobility syndrome); - neoplastic or post-neoplastic conditions (e.g., breast cancer). **Study Design:** • Narrative review[g], editorials[g,h], commentaries or expert opinion articles[g,h], point of view[g], brief communications[g,h], debate[g], perspectives[g], letters to editors[g,h], correspondences or replies to letters[g,h], book reviews or chapters[g], study protocol[h].

[a] *Or full text not in English language but with the abstract in English language.*
[b] *With a particular focus on studies reporting methodologies or test/measures feasible to translate in clinical practice.*
[c] *The correspondent paper were searched where available; included only if the abstract was available and if was described with a rigorous methodology and with clearly reported results on the base of the construct analyzed.*
[d] *Included only if it was described with a rigorous methodology, with clearly reported results on the base of the construct analyzed.*
[e] *Included studies and reference lists of secondary studied were manually scanned in order to find additional sources.*
[f] *Excluded from the analysis but reported in order to provide a general overview of the amount of international literature published.*
[g] *Reference list of records of interest for the topic were be manually scanned.*
[h] *Included in qualitative analysis only if containing additional information to an earlier or ongoing trial study report, or information about a study or experiment not reported elsewhere.*

A second author (DP) performed the crosschecking of data extracted. Information extracted from each study are detailed in **Supplementary Files** of the published study protocol. With respect to the original data-extraction form, the item "Future research direction" was deleted because it was not considered relevant The difference between groups means was used as an unstandardized measure for the size of the effect in intervention studies: in case of missed aggregated data, pooled mean and pooled standard deviation were calculated, as well as the 95% Interval Confidence (95% CI). The assessment of studies for clinical relevance was based on the Minimal Clinically Important Difference (MCID) thresholds established in literature for the outcomes used in included studies (see notes of the **Supplementary Table S2**).

Critical Appraisal of Individual Sources of Evidence

The primary goal of scoping studies is to systematically map and synthesize results coming from an emerging research area (Canadian Institutes of Health Research, 2010; Colquhoun et al., 2014), rather than provide the best available evidence. Considering also the methodological heterogeneity expected from the studies published on this topic, a qualitative appraisal for risk of bias was not conducted, in accordance to published guidelines on the conduct of scoping reviews (Peters et al., 2015).

Clinical Relevance of Studies Included in Qualitative Analysis

Clinical relevance was assessed by one author (AV) using the recommendations of the Cochrane Collaboration Back Review Group (Furlan et al., 2009) (a description of the items is provided in **Supplementary Table S2**). For evaluation studies, the item "Are the likely treatment benefits worth the potential harms?" was replaced with a "The involved procedure/s and/or setting are accessible in terms of cost and advanced technical knowledge required?" and the item "Are the interventions and treatment settings described well enough so that you can provide the same for your patients?" was replaced with "Are the settings and/or the methodology adopted, described well enough so that you can provide the same for your patients?". Finally, referring to case-controls studies, the item "Is the size of the effect clinically important?" was substituted with "Are there clinically significant differences in the population investigated respect to the control group/s?" In studies without control groups it was used the item "Is there a correlation of the dysfunction detected with at least one out the two clinical variables of pain and disability?" **Figures 7**, **8** summarize the evaluation for clinical relevance, respectively for assessment and for intervention studies.

RESULTS

Study Selection

A summary of the main findings is presented in **Tables 3**, **4**, organized with the acronym PCC-Population-Concept-Context (more detailed data can be found in **Additional Materials**).

The first calibration test was conducted on 239 titles and abstracts, and the second on 12 full-texts: the inter-rater agreement was, respectively, of 93 and 100%, and was reached for both procedures at the third round, at the end of which the reviewers express no need of further training. The search strategies initially produced 7,818 records from all the databases, and 13 from authors' personal databases (Morone et al., 2012; Paolucci et al., 2012, 2016; Wand et al., 2013a; Hirakawa et al., 2014; Louw et al., 2017; Stanton et al., 2017, 2018; Adamczyk et al., 2018a,b; Ehrenbrusthoff et al., 2018; Magni et al., 2018; Nishigami et al., 2019). After removal of duplicates and exclusion of clearly irrelevant records on the basis of the title and abstract, 123 full-texts were screened. Five full-texts were not found and 96 were excluded with reasons (see the **Supplementary Table S7**). Ten additional studies (Grod and Diakow, 2002; Barker et al., 2008; Wand et al., 2010, 2011; Preston and Newport, 2011; Nishigami et al., 2012; Diers et al., 2013; Ryan et al., 2014; Treleaven and Takasaki, 2015; Beales et al., 2016) were identified and considered eligible by searching the reference lists of included papers and reviews considered of interest for the aim of this work. Thirty-seven studies, analysing an overall sample of 1291 patients (1,094 in evaluation studies, and 197 for interventions ones), were included in the qualitative analysis and the end of the selection process (see the **Figure 2** for a flow-chart of the entire process). Agreement between raters in formal screening was 95% for titles/abstracts screening, and 91% in full-texts inclusion: all disagreements were resolved upon discussion and clarification of eligibility criteria, and the intervention of the third independent assessor (MT) was not needed. A graphical distribution of included studies grouped by clinical conditions examined is shown in **Figure 3**. Twenty-five studies (Grod and Diakow, 2002; Moseley, 2008; Wand et al., 2010, 2013b, 2014, 2016; Docherty et al., 2012; Lauche et al., 2012a; Valenzuela-Moguillansky, 2013; Hirakawa et al., 2014; Gilpin et al., 2015; Mibu et al., 2015; Nishigami et al., 2015, 2017, 2018; Treleaven and Takasaki, 2015; Beales et al., 2016; Janssens et al., 2017; Moreira et al., 2017; Adamczyk et al., 2018a,b; Ehrenbrusthoff et al., 2018; Magni et al., 2018; Martínez et al., 2018) studies concerned the assessment of SoP dysfunctions, while twelve interventional studies (Barker et al., 2008; Preston and Newport, 2011; Wand et al., 2011, 2013a; Morone et al., 2012; Paolucci et al., 2012; Diers et al., 2013; Vetrano et al., 2013; Ryan et al., 2014; Louw et al., 2017; Stanton et al., 2018; Nishigami et al., 2019) investigated the effects of perception-based intervention to reduce pain or to correct perceptual distortions. One study, (Lauche et al., 2012a) was included both in assessment and in intervention studies: it is a qualitative study investigating the explicit SoP in chronic neck pain (CNP) patients at baseline, and also at follow-up because it was embedded in a RCT study investigating the effect of cupping therapy (Lauche et al., 2012b). **Figure 4** displays the domains investigated by assessment and intervention studies.

Research Designs of Included Studies

The distribution of research designs adopted for assessment studies is graphically represented in **Figure 5**. A conspicuous number of these studies is composed by those validating the Fremantle Back Awareness Questionnaire (FreBAQ) (Wand et al., 2014) and the Fremantle Knee Awareness Questionnaire (FreKAQ) (Nishigami et al., 2017), including validation studies into other languages (Janssens et al., 2017; Ehrenbrusthoff et al., 2018; Nishigami et al., 2018), and cross-sectional or case-control investigations across different clinical samples (Wand et al., 2013a, 2016; Beales et al., 2016). **Figure 6** shows the research designs adopted in the intervention studies included, of which a large part were pre-clinical experimental studies (Diers et al., 2013; Nishigami et al., 2019).

Assessment Studies

Five studies were conducted in an experimental setting (Grod and Diakow, 2002; Docherty et al., 2012; Gilpin et al.,

TABLE 3 | Synopsis of included assessment studies.

Study	Design	Population	Concept and core outcomes	Context and main results
CLINICAL SETTING STUDIES				
Superficial schema (tactile localisation task)—implicit somatoperception				
Wand et al. (2013a)	Case-control Study	CLBP patients ($n = 24$) Healthy controls ($n = 24$)	11-NRS (0–10), RMDQ (0–24), Localization task for tactile and painful stimuli (n° of mislocalizations).	67% of subjects with CLBP reported at least 1 mislocalization with respect to 25% of controls (**$p = 0.034$**). Of the possible maximum 28 mislocalizations, five were reported in the worst cases by patients and three by controls. Correlation Analysis: no significant SD were found between mislocalizations errors and other variables, as Pain and Disability.
Model of body size and shape, and postural schema (body size perception and tactile localization task)—implicit somatoperception				
Adamczyk et al. (2018a)	Two-Case Report Study	CLBP ($n = 2$)	11-NRS (0–10), ODI (0–100%), 2-PET (mm) for subject A and B; PTP test (mm) for subject A; qualitative version of the PTP test for subject B.	Patient A) overestimated the painful site compared to all non-painful locations 2-PET; range: 45–206%, and also at PTP test: 24–84%. Subjects, by contrast, underestimated the distance at the 2-PET; range: 12–22% smaller than contralateral side.
Model of body size and shape (body size estimation)—implicit somatoperception				
Adamczyk et al. (2018b)	Preliminary Validation Study	CLBP patients ($n = 20$)	11-NRS (0–10), ODI (0–100%), Two-Point Estimation (TPE) Task (manual and verbal version).	CLBP patients underestimated the caliper distance by 56.2% (manual version) and 45.9% (verbal version), irrespective of the examiner and location. Reliability: the manual version was more reliable than the verbal one: Inter-rater agreement: manual TPE (ICC = 0.75–0.91); verbal TPE (ICC: 0.53–0.88). Measures in manual version reach a stability after two repetition at painful side: ICC = 0.91 (0.77–0.97). Inter-examiner agreement was god to excellent for manual version (ICC = 0.75–0.91). Intra-rater agreement was good to excellent both at two-day interval (ICC = 0.75–0.91) and at 10-min interval (ICC = 0.66–0.96). In regression Analysis pain duration and pain intensity accounted for 42% of the total variance.
Model of body size and shape (letter recognition task)- implicit somatoperception				
Wand et al. (2010)	Case-control Study	CLBP patients ($n = 19$) Healthy controls ($n = 19$)	11-NRS (0–10), SF-36: item 3—physical function (10–30), Letter recognition error rate (n°).	Letter error rate were significantly larger in CLBP group of about 10% (**$p = 0.016$**). No significant correlations were found between Letter error rate and 2-PDT in LBP group (raw data N.R.), nor between Letter error rate and any clinical data ($p>0.094$).
Depictive methods (body image drawings)—explicit somatoperception				
Moseley (2008)	Exploratory case-control study	CLBP patients ($n = 6$) Subjects with upper limb pain ($n = 10$)	101-VAS (0–100 mm), Clinical interview and Body Image Drawing of the trunk.	Five out of the six patients reported difficulties in delineating the full extent of their trunk: they all verbatim refer that they "can't find it." Two subjects reported that "It feels as though it has shrunk." No patients drew all vertebrae and missing vertebrae coincided with the level of the lost trunk delineation and of the usual pain. There was a tendency of vertebrae displacement from the midline in body drawings.
Lauche et al. (2012a)	a) Qualitative study embedded in a RCT (Lauche et al., 2012b)	CNP patients ($n = 6$)	Themes and sub-themes emerged from interviews in which patients were asked to talk about their body image drawings, Visual interpretation of the Body Image Drawing for neck and shoulders (modified version of that described by Moseley, 2008).	Interviews: patients refer changes in body perception of the neck as a feeling of swollen or distorted in proportion. These overestimations persist even when patients were aware of their actual appearance. Body Image Drawing: at the baseline, the drawn body showed noticeable discrepancies respect to a "normal" body (missing lines and augmented dimension of shoulders and neck) in 4 out 6 subjects more symmetric and complete.

(Continued)

TABLE 3 | Continued

Study	Design	Population	Concept and core outcomes	Context and main results
Mibu et al. (2015)	Case-control study	CNP patients ($n = 20$) Healthy controls ($n = 20$)	101-VAS (0–100 mm), Visual interpretation of the Body Image Drawing for neck and shoulders (modified version of that described by Moseley, 2008).	Body image is significantly (**$p = 0.0017$)** distorted in neck pain patients (50%) than in healthy controls (5%).
Nishigami et al. (2015)	Case-control study	CLBP patients ($n = 42$) Healthy controls ($n = 17$)	101-VAS (0–100 mm), RMDQ (0–24), Body Image Drawing of the trunk as described by Moseley (2008). Moreover, subjects were asked to judge the perceived image of their trunk as "normal," "expanded," or "shrunken."	42.8% of subjects with CLBP had a normal perceive image of the lower back, 28.5% had an expanded image, and 28.5% had a shrunken image. There was no significant differences for VAS scores, pain duration, RMDQ, and PCS scores between three perceived image subgroups; $p > 0.127$.
Moreira et al. (2017)	Exploratory case-control Study	CNP patients ($n = 7$) Healthy controls ($n = 7$)	11-VAS (0–10 mm), Modified version of the Body Image Drawing of the trunk as described by Moseley (2008).	Qualitative analysis of the body image drawing: In both groups, two subjects were not able to draw one side of the neck: comparing the drawings it seems that patients delineate neck and shoulders outline less symmetric and uniform than controls, and necks appear shorter. Moreover, two participants drew neck and shoulders more enlarged than they really were, and these perceptions coincided with pain location. Participants that not draw part of the neck, or drawing a clearly distorted neck tend to report pain of higher level and/or duration.
Qualitative studies—explicit somatoperception				
Valenzuela-Moguillansky (2013)	Qualitative Study	FM patients ($n = 12$)	Themes and sub-themes.	Interviewees refer modifications in different aspects of body perception: body size, weight, localization and ownership. They talk about enlarged, thicker and heavy body parts. They also refer that near space is perceived as smaller, as if it was shrinking while their body become larger. At the peak of the pain stage some patients described the perception that the painful body parts did not belong to them (loss of the sense of body ownership), expressing the paradoxical experience of being in extreme pain while not feeling it. Moreover, they refer the inability to localize their painful body parts and pain.
FreBAQ—explicit somatoperception				
Wand et al. (2014)	Psychometric Validation Study	CLBP patients ($n = 51$) Healthy controls ($n = 51$)	101-VAS (0–100 mm), RMDQ (0–24), FreBAQ (0–36).	Fifty of 51 (98%) CLBP patients endorsed some level of distortion in self-perception, with only one subject recording zero for all items. FreBAQ mean total mean score in CLBP patients was 10.8 (range = 0–26), in healthy subjects was 0.5; Median Difference: 11; **$p < 0.001$.** FreBAQ score was clinically correlated with pain duration [$\rho = 0.357$), pain intensity [$r = 0.400$] and disability [[$r = 0.365$]: overall **$p < 0.05$.**
Wand et al. (2016)	Cross-sectional Study	CLBP patients ($n = 251$)	11-NRS (0–10), RMDQ (0–24), FreBAQ (0–36).	FreBAQ mean total score in CLBP patients was 9.8 (SD = 6.6); median score = 9.0 (IQR = 4.0–14.0) and it was correlated with disability (0.319; **$p < 0.001$**) and pain intensity (0.265); **$p < 0.001$**) in bivariate association**.
Beales et al. (2016)	Case-control questionnaire based study	Post-Partum LPP patients ($n = 24$) Women with no post-pregnancy pain ($n = 26$)	Short-form MGPQ (0–45), ODI (0–100%), FreKAQ (0–36)	FreBAQ median difference: 6 (‡) between Moderate Disability sub-groups and pain free controls; **$p = 0.02$**; Difference in others group comparison were not statistically significant
Wand et al. (2017)	Exploratory cross-sectional questionnaire based study	Pregnancy-related LPP patients ($n = 42$)	11-NRS (0–10), PGQ (0–100), FreBAQ (0–36).	FreBAQ median difference between pain and pain-free groups: 2.5; (‡); **$p = 0.005$.** FreBAQ score was significantly associated with pain intensity ($r = 0.378$; **$p = 0.027$**) but not with disability ($r = 0.256$; $p = 0.143$).

(Continued)

TABLE 3 | Continued

Study	Design	Population	Concept and core outcomes	Context and main results
Nishigami et al. (2018)	Psychometric Validation Study	CLBP patients ($n = 100$)	101-VAS (0–100 mm), RMDQ (0–24), FreBAQ (0–36).	FreBAQ mean total score in CLBP patients was 11.7 (6.4), and it was significantly correlated with pain in motion ($\rho = 0.25$) and disability ($\rho = 0.36$), **overall $p < 0.05$**. The questionnaire showed excellent 2w Reliability ($n = 40$): $ICC_{3,1} = 0.81$ (0.67 to 0.89).
Janssens et al. (2017)	Psychometric Validation Study	CLBP patients ($n = 73$) Healthy controls ($n = 73$)	11-NRS (0–10), ODI (0–100%), FreBAQ (0–36).	FreBAQ mean total score in CLBP group ($n = 73$) was 11 points (7) and median score = 3 (IQR = ±9) in control group ($n = 73$); **$p = 0.001$**. Sub-groups analysis revealed that patients with higher disability (ODI ≥20%) scored significantly higher on FreBAQ with respect to those with lower level (ODI <20%: 13 (8) vs. 8 (6); **$p = 0.005$.** FreBAQ was significantly correlated with ODI (rho = 0.30; **$p = 0.010$**). The reliability on 1-w interval was moderate ($ICC_{2,1} = 0.69$; 0.51 to 0.82), however the MDC (95%) was the 30% of the scale (10.8 points), referring to a non-sufficient measurement error.
Ehrenbrusthoff et al. (2018)	Psychometric Validation Study	CLBP patients ($n = 35$) Healthy controls ($n = 48$)	Short Form BPI: Pain Severity (0–10), Pain Interference (0–7), RMDQ (0–24), FreBAQ (0–36).	Global FreBAQ mean total score was significantly different in CLBP group ($n = 35$) respect to control group ($n = 48$): 8.8 (6.1) vs. 4.0 (3.3); **$p = 0.001$.** MD adjusted for Age, Gender and BMI = 5.4 (3.0 to 7.8); **$p < 0.01$.** The 1w-Reliability and Inter-observer reliability were good: ICC for absolute agreement were, respectively, 0.88 (95% CI: 0.77–0.94) and 0.88 (95%CI: 0.75–0.94). FreBAQ score was significantly correlated with Pain (BPI-Pain Interference: $rs = 0.47$; **$p < 0.001$**) and Disability (RMDQ: $rs = 0.46$; **$p < 0.001$**).
FreKAQ—explicit somatoperception				
Nishigami et al. (2017)	Psychometric Validation Study	Knee OA patients ($n = 65$) Healthy subjects ($n = 65$)	101-VAS (0–100 mm), OKSQ (0–48), FreKAQ (0–36)	FreKAQ mean total score was significantly higher in knee patients vs. healthy controls: 12.4 (7.6) vs. 3.4 (4.4); (**$p = 0.001$**). The reliability at 2 w was good ICC ($n = 23$): 0.76 (0.52 to 0.89). FreKAQ score was significantly correlated with Pain during motion (101-VAS: rho = 0.37; **$p = 0.002$**) and Disability (OKSQ: rho = −0.41; **$p = 0.001$**).
Neglect-like symptoms questionnaire—explicit somatoperception				
Magni et al. (2018)	Case-Control Study	Hand OA Patients ($n = 20$) Healthy subjects ($n = 19$)	11-NRS (0–10), DASH (0–100), NLSQ (5–30).	The hand OA group reported neglect-like symptoms (median score: 5.5; IQR: 3) significantly (**$p < 0.001$**) more often than the control group (median score: 5; IQR: 0), however the difference was very low: 0.5 points (‡); $\chi^2(1)=12.8$; Cramer's V =0.6.
Hirakawa et al. (2014)	Longitudinal Study	Total Knee Arthroplasty for Knee OA patients ($n = 90$)	101-VAS (0–100 mm), NLSQ (0–500): Motor Neglect (MN) and Cognitive Neglect (CN) sub-scales.	The percentage of patients with a total NLSQ ≥100 was 36% (MN, 40%; CN, 18%) at 3 w and 19% (MN, 19%; CN, 5%) at 6 w. The MN subscale of NLS was associated with Pain at 3 w ($\beta = 0.50$; **$p < 0.01$**) and 6w ($\beta = 0.53$; **$p < 0.01$**). The total score of NLSQ (for both MN, and CN sub-scales) decreased at 6 w from 77.7 (87) to 41.2 (62.1); Cronbach's $\alpha \geq 0.92$ (+) for the total score; however, the SD was high, indicating a large variation among patients.
EXPERIMENTAL SETTING STUDIES				
Visual estimation task—explicit somatoperception				
Gilpin et al. (2015)	Case-control Study	Hand OA patients ($n = 12$) Healthy controls ($n = 12$)	Visual size estimation task (% of the real hand size).	Hand size estimations were significantly smaller for the OA group: −8.01 (3.07 to 12.94); $t(22) = 2.39$, **$p = 0.026$,** indicating an underestimation of hand dimensions.

(Continued)

TABLE 3 | Continued

Study	Design	Population	Concept and core outcomes	Context and main results
RHIP—body ownership				
Martínez et al. (2018)	Case-control Study	FM patients ($n = 14$) Healthy controls ($n = 13$)	11-VAS (0–100 mm), Short-form BPI (0–20), FIQ (0–100), 5-point Likert Scale measuring proprioceptive drift (0.35), ownership (0–35) and agency (0–30).	FM patients were more prone to experiment the misperceptions produced by the RHIP. They scored significantly (***p* < 0.05**) higher in all 5-items of the proprioceptive drift scale and in 4 out 5 items of the agency scale (Effect Size varying between 0.88 and 3.10): differences were largest in the proprioceptive drift domain, where large effect sizes were found across all items.
Perception of subjective visual vertical/ horizontal—extra-personal space perception				
Treleaven and Takasaki (2015)	Case-control Study	CNP patients ($n = 36$) WAD patients ($n = 42$) Healthy controls ($n = 48$)	11-NRS (0–10), NDI (0–100%), Short Form DHI (0–13), SVV: Computerized Rod And Frame (CRAF) test as described by Takasaki et al. (2012). Error calculation: mean AE (°), mean VE (°), mean CE (°), mean RMSE (°).	CNP group had significantly larger variability of SVV errors vs. the other two groups: 1) VE = 0.5 (0.23 to 0.77) vs. healthy controls (***p* = 0.001**); 0.37 (0.07 to 0.67) vs. WAD (***p* = 0.02**); 2) RMSE = 0.51 (0.09 to 0.93) vs. healthy controls (***p* = 0.01**); 0.58 (0.20 to 0.96) vs. WAD (***p* = 0.01**). The AE and DE were not able to detect group differences (*p*-value respectively of 0.06 and 0.99). Despite the higher level of disability of the WAD group, there were no significant differences in SVV error between this group and healthy subjects ($p = 0.91$). SVV errors and Disability (DHI) seemed to be unrelated, where a sample of the scatter plot for VE is presented (raw data N.R.).
Docherty et al. (2012)	Case-control Study	CNP patients ($n = 50$) Healthy controls ($n = 50$)	11-NRS (0–10), NDI (0–50), SVV and SVH: Computerized Rod And Frame (CRAF) test (°).	In absence of surrounding frame, significant difference were found in mean errors (***p* < 0.05**) both for SVV and SVO test between groups, however they fell within a range considered normal (<0.5°). Significant between-groups difference both for the SVV and SVO (***p* < 0.001** in all cases) was recorded in tilting the frame clockwise or counter clockwise by 18°, although the difference between the medians values for these tests were still small (<2°). Of the 50 CNP patients, a subgroup of 8 subjects (16%) exhibited higher than normal errors in both the SVV and SVO: these patients scored higher on the NDI than patients whose errors fell within the reference range ($U = 74.0$, $p < 0.016$).
(Grod and Diakow, 2002)	Cohort study	Acute or recurrent NP patients ($n = 19$) Healthy controls ($n = 17$)	Computerized Rod And Frame (CRAF) test as used by Docherty et al. (2012). SVV (°) and SVH (°).	Statistically significant differences in SVV and SVO were found between symptomatic and asymptomatic subjects (F = 13.37, p = **0.001**); pooled Mean Difference = 1.99° (pooled SD = 1.61).

*ACR, American College of Rheumatology; CLBP, Chronic Low Back Pain; LPP, Lumbo-Pelvic Pain; FM, Fibromyalgia; OA, Osteoarthritis; NP, Neck Pain; CNP, Chronic Neck Pain; VAS, Visual Analog Scale; NRS, Numeric Rating Scale; Chronic Pain Grade, CPG; BPI, Brief Pain Inventory; MGPQ, McGill Pain Questionnaire; ODI, Oswestry Disability Index; RMDQ, Roland Morris Disability Questionnaire; DASH, NDI, Neck Disability Index; DHI, Dizziness Handicap Inventory; BPQ, Body Perception Questionnaire; Disabilities of the Arm, Shoulder and Hand Questionnaire; PGQ, Pelvic Girdle Questionnaire; TSK, Tampa Scale of Kinesiophobia; PCS, Pain Catastrophizing Scale; FPQ, Fear of Pain Questionnaire; HADS, Hospital Anxiety and Depression Scale; BDI, Beck Depression Inventory; DASS, Depression Anxiety Stress Scale; STAI, State-Trait Anxiety Inventory; FIQ, Fibromyalgia Impact Questionnaire; SIQ, Symptoms Impact Questionnaire; OKSQ, Oxford Knee Score Questionnaire; MAIA, The Multidimensional Assessment of Interceptive Awareness; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; PU, Pain Unpleasantness; PI, Pain Intensity; PeT, Perception Threshold; PT, Pain Threshold; PTo, Pain Tolerance; FreKAQ, Fremantle Knee Awareness Questionnaire; NLSQ, Neglect-like symptoms questionnaire, TPT, Tactile Perception Threshold; 2PDT, 2-Point Discrimination Threshold; PTP, Poin-to-Poin Test; 2-PET, two Point Estimation Test; ROM, Range Of Motion; JPS, Joint Position Sense; TEMPA, Test d'Evaluation de la performance des Membres Supérieurs des Personnes Agées; BMI, Body Mass Index; RHIP, Rubber Hand Illusion Paradigm; SVV, Subjective Visual Vertical; SVH, Subjective Visual Horizontal; AE, Absolute Error; VE, Variable Error; AE, Absolute Error; VE, Variable Error; AE, Absolute Error; VE, Variable Error; DE, Direction of Error; RMSE, Root Mean Square Error; MDC, Minimal Detectable Change; ICC, Interclass Correlation Coefficients; MD, Mean Difference; NR, not reported; NA, Not Applicable; SD, Standard Deviation; IQR, Interquartile Range; SEM, Standard Error of Measurement; CI95%, Confidence Interval; +, p-value not reported; ‡, 95% CI not reported; SD, statistical difference; y, year/s; m, month/s; h, hour/s, min., minute; s, second/s, ms, millisecond. **p-value** is reported in bold if statistically significant; **sub-groups were obtained through the median split with established ODI categorisation.*

TABLE 4 | Synopsis of included intervention studies.

Study	Design	Population	Concept and core outcomes	Context and main results
CLINICAL SETTING STUDIES				
Tactile localization training—implicit somatoperception				
Wand et al. (2013b)	Randomized COT	CLBP patients ($n = 24$)	1) Patients were assigned to: 2) acupuncture treatment involving sensory discrimination training (single session); a true acupuncture treatment (single session); 11-NRS (0–10) after performing 10 repeated spine movement in the most provocative direction reported in the initial physical examination.	a) Pain was significantly lower in both groups at the end of treatment, regardless of treatment order ($p = 0.182$), but the magnitude of pre-post treatment change was not clinically significant: 11-NRS = −0.9 (−0.3 to −1.5), $p =$ **0.008.** b) Pain was lower in EG but the magnitude of change was not clinically relevant: 11-NRS: −0.8 (−1.4 to −0.3) in favour to EG, ***p* = 0.011.**
Louw et al. (2017)	Case-series	CLBP patients ($n = 16$)	It was administered a perceptual localization task of 5 min. in a single session. 11-NRS (0–10), Functionality: active lumbar flexion (cm), FABQ (0–92).	a) Pain was lower after treatment (11-NRS: –**1.9**; (‡) range: 0 to 6; +) but the magnitude of pre-post treatment change was not clinically significant. Functionality improves after treatment with clinical significance (**4.8**; ‡; range: −1 to 21; +).
Barker et al. (2008)	Single-blinded, RCNIT	CLBP patients ($n = 60$)	It was tested the non-inferiority of the FairMed (device for sensory discrimination training), administered for 30 min (twice a day, for 3 weeks), respect to the TENS (same dosage). 0–11 VAS (0–10 mm) as a mean of patients' present pain intensity level, their average and worst pain intensity levels recorded over a week, ODI (0–100%), Physical Functioning: 5 min walking distance (5'-WD), 1 min stair climb (1'-SC) and 1 min sit-to—stand (1'-STS).	a) Both groups improved in pain scores: 0–11 VAS = −0.8 (−1.5 to −0.1) for EG; –**7.3** (−8.1 to −6.6) for CG but the differences were not statistically significant ($p = 0.83$). The same positive trend was recorded for disability: ODI = −0.6 (−3.8 to 2.7) for EG, and −0.9 (−3 to −1.1) for CG. Even in this case the difference was neither statistically ($p = 0.85$), nor clinically significant. All other functional measures (5'-WD, 1'-SC, 1'-STS) improved in both groups, without statistically significant difference between pre- and post- recordings ($p>0.05$). FairMed device was not inferior respect to TENS. There were minimal and no statistically significant difference between groups both for pain (0–11 VAS: −0.1; −0.7 to 0.3; $p = 0.82$) and disability (ODI: 0.4; −0.7 to 0.4; $p = 0.85$). The same trend was recorded for all the other functional measures 5'-WD, 1'-SC, 1'-STS, without statistically significant differences.
Mixed perceptual training (graded perceptual training + graded motor retraining)—implicit somatoperception				
Wand et al. (2011)	Three single-case study	CLBP patients ($n = 3$)	It was tested a mixed treatment program composed by education and graded perceptual retraining program (localization and graphaesthesia training) combined with graded motor retraining (minimum 10 w of home exercises). 11-NRS (0–10), RMDQ (0–24).	Both Pain and Disability improves with clinical and statistical significance: 11-NRS = –**2.9**; (1.2 to 4.6) at T1; ***p* < 0.001**; –**3.9**; (1.6 to 6.2) at T2; ***p* < 0.001;** RMDQ = –**5.2** (2.4 to 8) at T1; ***p* < 0.001**; –**9.6** (4.2 to 15) at T2; ***p* < 0.001.**
(Ryan et al., 2014)	Mixed-methods pilot RCT	CLBP patients ($n = 24$)	Patients were assigned to: 1) EG: combined tactile acuity and graphaestesia acuity training as used by Wand et al. (2011), plus usual physiotherapy (3 sessions + 21 at home); 2) CG: tactile stimulation alone (placebo) plus usual care (same dosage). 101-VAS (0–100 mm), RMDQ (0–24).	Tactile acuity training was not superior to sham therapy. Both groups improved pain and disability post-treatment but only values for CG were statistically significant (101-VAS: –**33.2**, CI95%: −58.3 to −8; RMDQ: –**4**; CI95%: −6.7 to −1.3); ***p* < 0.05).** Between-groups comparison was in favour to sham group both for both 101-VAS (25.6; −0.7 to 51.9) and RMSQ (2.2; −1.6 to 6.0), despite with no statistical significance ($p = 0.056$ and $p =$ 0.237 respectively).

(Continued)

TABLE 4 | Continued

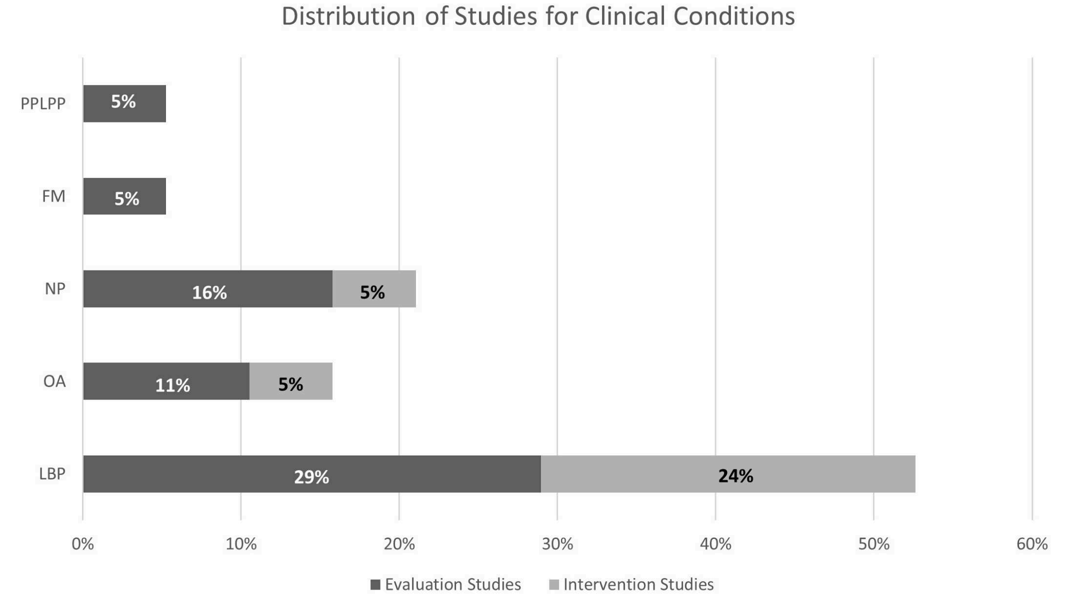
Study	Design	Population	Concept and core outcomes	Context and main results
Mixed perceptual training (SuPerR Treatment)—implicit Somatoperception				
Morone et al. (2012)	Single-blinded, RCT	CLBP patients ($n = 75$)	Patients were assigned to: 1) EG: SuPeR treatment (perceptive surface plus active exercises, 45', 3 x week for 1 month, and usual pharmacological care); 2) CG1: Back school program (10 session for 1 m, and usual pharmacological care), CG2: Medical and pharmacological assistance only (as the other two groups). 11-VAS (0–10 mm), ODI (0–100) post-treatment (T1), at 12 w (T2) and 24 w (T3).	Both groups treated with SuPeR and with Back School obtain an overall improvement both for Pain and Disability at T1 and T3: 11-VAS = –**2*** (‡) (**$p < 0.001$**) at T1 and T3 for EG; −1* (‡) at T1 and –**3*** (‡) at T3 (**$p < 0.001$**) for CG; ODI = –**18*** (‡) at T1 and –**14*** (‡) at T3 for EG; −10* at T1 (‡) and –**16*** (‡) at T3 for CG (**$p < 0.001$**). CG2 maintained substantially unaltered the level of Pain and Disability at T1 and T3 ($p>0.05$). EG patients recorder statistically less Pain at T1 respect to CG1 (11-VAS: −1*; ‡) and CG2 (11-VAS: –**3***; ‡) (**$p < 0.001$**), but at T3 the improvement was in favour to CG1 (11-VAS: 2*; ‡; **$p < 0.001$**), despite the magnitude of the effect was not clinically relevant. The effect of the EG for Disability at T1 was not statistically different respect to CG1 and CG2 ($p = 0.403$). At T3 EG reduced Disability significantly lower than CG2 (ODI: –**16***; ‡; **$p = 0.023$**), but no difference was found respect to CG2 (ODI: −2*; ‡); ($p = 0.169$).
Paolucci et al. (2012)	Single-blinded, RCT	CLBP patients ($n = 45$)	Patients were assigned to: 1) EG: SuPeR: the same protocol of Morone et al. (2012); 2) Back school program with: the same protocol of Morone et al. (2012). MGPQ (0–78).	The SuPereR treatment reduce pain more than the CG performing the Back School program, but the difference was not statistically significant: MGPQ = 44±24% for EG† and 39±15% for CG†; $p =$ 0.436. †Authors reported the % improvement with respect to the maximum achievable improvement.
Vetrano et al. (2013)	Single-blind, RCT	CLBP patients ($n = 40$)	Patients were assigned to: 1) EG: modified SuPeR treatment (more deformable cones at midline level, decreasing tactile-pressure inputs at midline level and without taking consciousness of the body midline; 2) Standard SuPeR treatment: the same protocol of Morone et al. (2012) but with 5' less of treatment duration and with an increase of tactile-pressure inputs at midline level. 11-VAS (0–10 mm), ODI (0–100), post-treatment (T1), at 4 (T2) and 12 weeks (T3).	Both groups improved pain and disability scores at T1 and T3 respect to the baseline: 11-VAS: −2* (‡) at T1, –**3*** (‡) at T3 (**$p < 0.001$**); ODI: –**14*** (‡) at T1, –**20*** (‡) at T3 (**$p < 0.001$**) for EG. 11-VAS: –**2.5*** (‡) at T1, –**5.5*** (‡) at T3 (**$p < 0.001$**); ODI: –**16*** (‡) at T1, –**21*** (‡) at T3 (**$p < 0.001$**) for CG. The modified SuPerR treatment was substantially as effective as the standard version both for pain and disability: 11-VAS and ODI scores were lower for CG at T1 and T3 but differences were not statistically significant: 11-VAS: −2* (‡) at T1 ($p = 0.179$), 2.5* (‡) at T3 ($p =$ 0.868); ODI: 2* (‡) at T1 ($p = 0.299$), 1* (‡) at T3 ($p = 0.922$).
Qualitative Studies—Explicit Somatoperception				
Lauche et al. (2012a)	Qualitative study embedded in a RCT (Lauche et al., 2012b)	CNP patients ($n = 6$)	Patients were interviewed before and 3 d after a single traditional cupping treatment (for half of the patients); the other half of patients were in waiting list. Themes and sub-themes emerged from interviews in which patients were asked to talk about their body image drawings, Visual interpretation of the Body Image Drawing (modified version for trunk as described by Moseley, 2008).	Interviews: subjects in EG refer a reduction in neck size (smaller) as a relief from pain. Body Image Drawing: Body image appears to be changed in EG after treatment (smaller dimension of body parts, and lines more symmetric and complete). Even the CG subjects improve in drawings their own's body, but they were no more complete, nor matched a "normal" silhouette.

(Continued)

TABLE 4 | Continued

Study	Design	Population	Concept and core outcomes	Context and main results
Experimental Study				
Manipulation of visual body appearance—Explicit Somatoperception				
Preston and Newport (2011)	Exploratory experimental study	Hand OA patients ($n = 20$)	Patients were administered the MIRAGE system: visuo-tactile illusion involving manipulations (stretching or shrinking) of patient's hand (affected and unaffected) while experimenter gently pulling or pushing on part of the hand. 21-NRS (0–20).	85% of patients reported reduction in pain for at least one of the experimental conditions (stretching and shrinking), but only manipulating visual appearance of the affected hand. For subjects in whom the stretching was beneficial the condition produced ∼50% on pain reduction (–**3.09**, ‡; +), while for those in whom the shrinking condition was beneficial pain decrease of ∼45% (–**2.68**, ‡; +).
Diers et al. (2013)	Experimental study	Bilateral TP patients ($n = 18$) Healthy Controls ($n = 18$)	Patients were administered: 1) EG: an on-line video feedback of the neck in enlarged and downscaled fashion; 2) CG: video feedback of neutral (hand dorsum) body part, and affected neck in unaltered fashion. PU for pressure stimulation applied to the TrP1 of the Trapezius muscle: 11-NRS (0–10), PU and PI for electrical stimulation applied to the TrP1 of the Trapezius muscle: 11-NRS (0–10).	There was no significant influence on Electric and Pressure PU ($p <$ 0.986) and PI ($p <$ 0.825) for back hand condition (CG). Visual feedback conditions (CG) significantly influenced the Electric and Pressure PU and PI: (***p* < 0.001**), in Downscaled, Enlarged and Size Control Back condition, even if the differences were never over the clinical significance.
Stanton et al. (2018)	Pilot-experimental study	Knee OA patients ($n = 12$)	Patients were administered the MIRAGE system as described in Preston and Newport (2011), applied to the knee in 8 conditions: congruent (CO) and incongruent (IN) X vision only (VO), tactile only (TO) and visuotactile (VT) X stretch (ST) and shrink (SR); 30s with 2 min. rest. Session 1: Total duration: 1 h. Session 2: the CO condition producing the greatest pain reduction was applied for 3 min (sustained condition-SU) and repeated for 10 trials (repeated condition-RE), minimum 2 w apart. Session 3: the RE condition of the Session 2 was repeated maximum 3 w apart. 101-NRS (0–100) immediately and 48h after Session 2, prior Session 3.	VT illusion decreased pain by an average of 7.8 points (2.0 to 13.5), corresponding to a 25% reduction in pain both in CO ($t_{1,11}$ =2.96, ***p* = 0.013**) and in IN conditions. SU condition prolonged analgesia, but did not increase it: (Session 1: $t_{1,10}$ =0.52, $p = 0.61$; Session 3: $t_{1,7=}$-0.697, $p = 0.51$). RE condition (with congruent VT illusion) increased the analgesic effect: 101-NRS: –**20** (−6.9 to −33.1), corresponding to a 40% pain reduction. Between Conditions Difference: The CO-VT condition did not differ from the IN-VT condition, controlled for vision: no effect of Condition ($F_{1,11}$ =0.032, $p = 0.86$), Condition x Time interaction ($F_{1,11} = 0.34$, $p = 0.57$), suggesting that analgesia was provided by both conditions when identical visual manipulations occurred; in contrast CO-VT reduce more pain than IN-VT when controlled for tactile input: Time effect ($F_{1,11}$ =5.23, ***p* = 0.043**), Condition x Time interaction ($F_{1,11} = 5.29$, ***p* = 0.042**).
Manipulation of visual body appearance + cognitive manipulation—explicit somatoperception				
Nishigami et al. (2019)	Pilot-experimental study	CLBP patients ($n = 2$)	Patients were administered the MIRAGE system as described in Preston and Newport (2011), applied to low back during a lifting task in three different conditions. Participants watched: a) a modified version of their back (muscled, fit-looking strong, back); b) - reshaped image of their back; c) a normal shaped condition 101-NRS (0–100), Fear: 101-NRS (0–100).	Visual illusion of a strong back vs. normal condition reduce pain and fear only in subject having distorted explicit perceptual representation of his back (FreBAQ: 29/36): 101-NRS for pain = –**30**; 101-NRS for fear: −12. No significant reduction for pain and fear in the second subject without distorted perceptual representation.

*ACR, American College of Rheumatology; CLBP, Chronic Low Back Pain; LBP, Low Back Pain; TP, Thoracic Pain; CNP, Chronic Neck Pain; OA, Osteoarthritis; MPQ, VAS, Visual Analog Scale; 11-NRS, 11-point Numeric Rating Scale; MGPQ, McGill Pain Questionnaire; ODI, Oswestry Disability Index; RMDQ, Roland Morris Disability Questionnaire; TSK, Tampa Scale of Kinesiophobia; RCT, randomized controlled trial; SuPeR, Surface for Perceptive Rehabilitation; TENS, Transcutaneous Electrical Nerve Stimulation; NSAIDs, Nonsteroidal Anti-Inflammatory Drug; TrP, Trigger Point; PU, Pain Unpleasantness; PI, Pain Intensity; PeT, Perception Threshold; PT, Pain Threshold; PTo, Pain Tolerance; RCT, Randomized Controlled Trial; COT, Cross-Over Trial; RCNIT, Randomized Controlled Non-Inferiority Trial; N.R., not reported; SD, Standard Deviation; MD, Mean Difference; CI95%, Confidence Interval; *, median difference; +, p-value not reported; ‡, 95% CI not reported; SD, statistical difference; y, year/s; m, month/s; h, hour/s; EG, Experimental Group; CG, Control Group. **p-values** are reported in bold if statistically significant; other values reported in **bold** if clinically significant based on the established Minimal Clinically Important Difference: for LBP was considered as clinically significant 13 points on the ODI (Copay et al., 2008; Johnsen et al., 2013), 30% on VAS/NRS for pain (Farrar et al., 2001; Ostelo et al., 2008), 2–3 points (or 8–12%) on the RMDQ for function (Bombardier et al., 2001; Ostelo et al., 2008) and 4.5 cm for the Active Lumbar Flexion (Ekedahl et al., 2012). For neck pain, was considered 3.5 to 5 U on the 50-U Neck Pain Disability Index or 7 to 10% change (Pool et al., 2007; Stratford et al., 2009) for function and 2.5 on an 10-U NRS (25% change) for pain (Pool et al., 2007).*



PPLPP: Post-Partum Lumbar-Pelvic Pain; FM: Fibromyalgia; NP: Neck Pain; OA: Osteoarthritis; LBP: Low Back Pain.

FIGURE 3 | Summary of the distribution of included studies for clinical conditions examined.

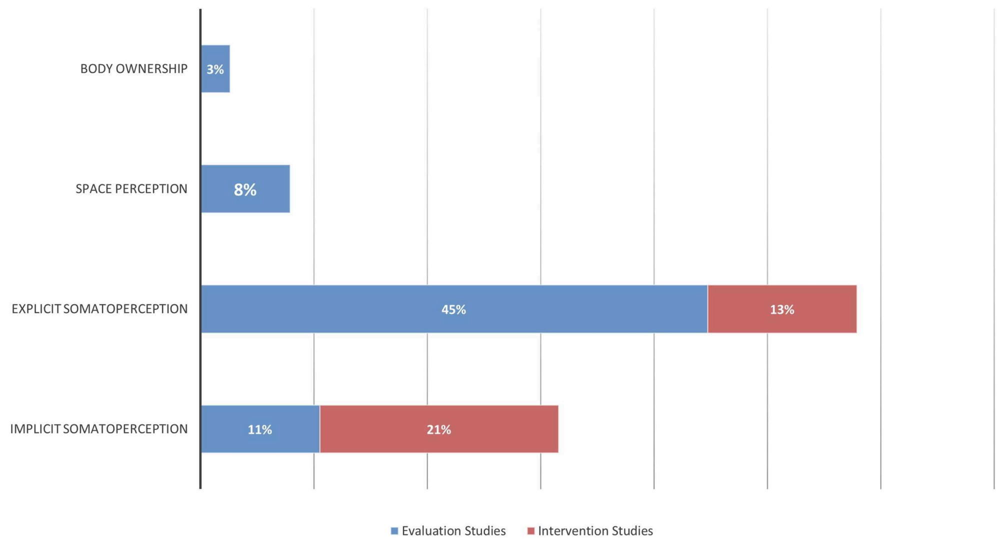


FIGURE 4 | Summary of the distribution of domain investigated for study typology.

2015; Treleaven and Takasaki, 2015; Martínez et al., 2018), while the remaining 19 studies were clinical investigations (Moseley, 2008; Wand et al., 2010, 2013a,b, 2014, 2016; Lauche et al., 2012a; Valenzuela-Moguillansky, 2013; Hirakawa et al., 2014; Mibu et al., 2015; Nishigami et al., 2015, 2017, 2018; Beales et al., 2016; Janssens et al., 2017; Adamczyk et al., 2018a,b; Ehrenbrusthoff et al., 2018; Magni et al., 2018).

The main domain studied was explicit SoP (58%; 22/38), followed by implicit SoP (32%; 12/38), and SpP (8%; 3/38), while the BO made up only the 2% (1/38) of the sample.

Implicit Somatoperception

Only 4/24 (17%) of the included assessment studies investigated implicit SoP. Adamczyk et al. (2018a,b) preliminarily validated a methodology for the objective evaluation of implicit body size

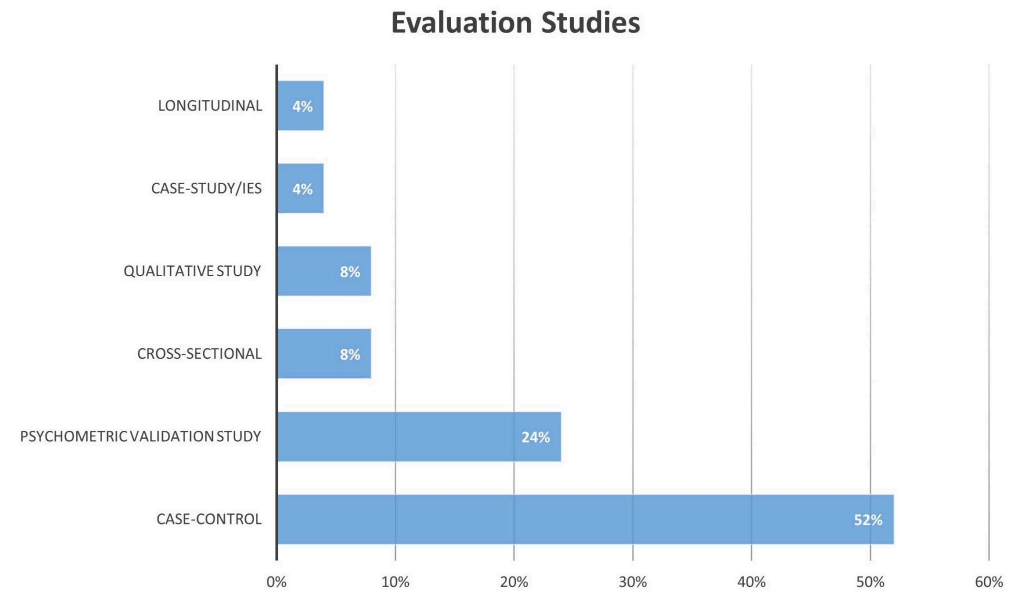
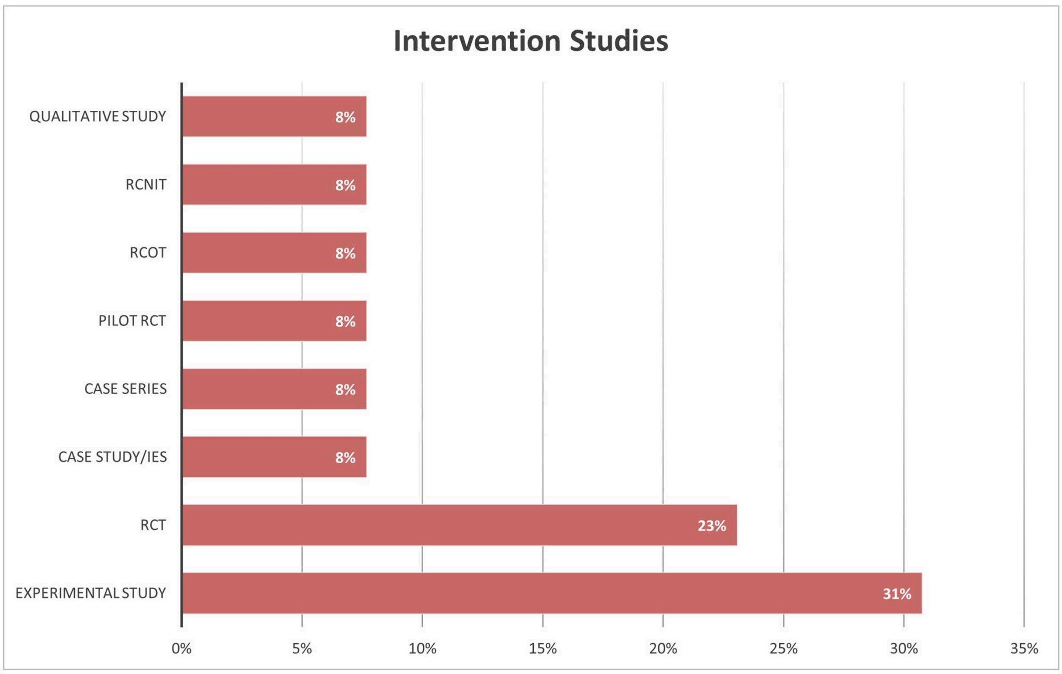


FIGURE 5 | Summary of the distribution of evaluation studies for research design adopted.



RCNIT: Randomized Controlled Non-Inferiority Trial; RCOT: Randomized Cross-Over Trial; RCT: Randomized Controlled Trial.

FIGURE 6 | Summary of the distribution of intervention studies for research design adopted.

perception, the two-point estimation (2-PET) task. Among all the included assessment studies, it is the only one adopting an objective methodology to assess metric features of SoP. Authors found an underestimation of the distance between two tactile stimuli delivered with a caliper on the back (46 and 56%, respectively on the verbal and manual version of test) in both the painful and pain-free low-back side. Duration and pain intensity predicted the presence of perceptual dysfunctions and accounted for the 42% of the total variance of 2-PET scores in the regression analysis. The same 2-PET task were used by the same authors in a two-case report study (Adamczyk et al., 2018a) in which one patient showed an overestimation of the painful side, compared to non-painful locations (range: 45–206%), while a second patient showed the opposite pattern with an underestimation ranging between 12 and 22%. In this double case-study, authors used also another test, the point-to-point test (PTP): the distance error between the site touched by the examiner and that touched by the patient was greater on the painful side than on the pain-free location, for a magnitude of 24–84%. With this second patient, the authors used also a qualitative version of the PTP test: subject were asked to point with a pen to the site stimulated by the examiner. In case of error, the examiner drew the error trajectories directly on the patient's back by moving the pen from the incorrect location indicated by the patient to the correct one: on the painful side all the trajectories were outside the referred symptomatic area and considerably spaced between them, indicating large errors in pointing the site of tactile stimuli.

Only one study (Wand et al., 2013b) adopted the localization task of tactile stimuli to assess the superficial schema. Subjects, after being stimulated by the experimenter with tactile and painful stimuli, were asked to mark on a body chart with 12 pre-defined areas of the trunk and thighs, the perceived localization of the applied stimuli. Authors found that 67% of chronic lower back pain (CLBP) patients made at least one localization error compared to only 25% of healthy controls, but no correlations were found between mislocalization errors and either pain and disability. Of the possible maximum 28 mislocalizations, five were reported in the worst cases by patients and three by controls. The study involved tactile and pinprick stimuli, but the authors reported combined results for both type of stimulations, without differentiating between types of task (*personal communication with authors*).

The Letter recognition task (or graphesthesia) involves the recognition of letters drawn on the skin. This task was tested only in the study of Wand et al. (2010): CLBP patients showed 10% more errors respect to healthy controls ($p < 0.05$), however this score was not correlated with clinical data.

Explicit Somatoperception

Body image drawing task

The majority of selected assessment studies evaluated the explicit SoP: five studies adopted the Body Image Drawing (BID) task (Moseley, 2008; Lauche et al., 2012a; Mibu et al., 2015; Nishigami et al., 2015; Moreira et al., 2017), eight studies used the FreBAQ (Wand et al., 2014, 2016; Wand et al., 2013a; Beales et al., 2016; Janssens et al., 2017; Nishigami et al., 2017, 2018; Ehrenbrusthoff et al., 2018) or the FreKAQ (Nishigami et al., 2017), two studies used the Neglect-Like Symptoms Questionnaire (NLSQ) (Hirakawa et al., 2014; Magni et al., 2018), one study investigate the visual size estimation in an experimental setting (Gilpin et al., 2015), one study investigated the rubber hand illusion (RHI) (Martínez et al., 2018), and one was a qualitative study on subjectively referred body perception (Valenzuela-Moguillansky, 2013).

Of the five study using the BID task, two were conducted on CLBP patients (Moseley, 2008; Nishigami et al., 2015) and three on Chronic Neck Pain (CNP) patients (Lauche et al., 2012a; Mibu et al., 2015; Moreira et al., 2017). All studies reported distortions in BID in a variable percentage of patients: Moseley (2008) found that five out of six patients with CLBP reported difficulties in drawing their trunk along all the entire extension. Four out of six showed the tendency to draw their vertebrae displaced from the midline toward the painful side. Moreover, two patients reported a feeling of shrunken trunk. In a larger sample of patients ($n = 42$), matched with 17 healthy controls, Nishigami et al. (2015) found distorted BID in about 50% of patients: half of them showed an enlarged image of their back, while the other half drew a shrunken BID. The other 50% of patients had a normal BID. However, the authors found no significant differences in pain intensity, duration, or disability between the three groups. Mibu et al. (2015) found a distorted neck drawing in 50% of patients with CNP (significantly more than the 5% of healthy controls), however there were no differences either for pain duration or intensity within CNP sub-groups, or with respect to healthy controls. Moreira et al. (2017) in their preliminary case-control study found a less symmetric and uniform outline of neck and shoulders in CNP patients than in controls. Two patients drew their neck and shoulders enlarged, while another two were unable to delineate one side of the neck, as well as two subjects in control group. Participants with a clearly distorted neck image or unable to draw body parts, tended to report higher pain intensity and duration. Finally, in the qualitative study of Lauche et al. (2012a) the authors used both interviews and BID. In four out six CNP patients, the qualitative analysis of the drawings showed noticeable discrepancies compared to a normal body silhouette, with missing lines and overestimated size of the neck and shoulders.

Visual size estimation procedure

Among the assessment studies analysing the subjective visual appearance of body parts, only that of Gilpin et al. (2015) was conducted in an experimental setting. Patients with hand osteoarthritis were asked to judge what photograph corresponded to their actual hand. Photographs were experimentally manipulated in percentage of the real length dimension: patients significantly underestimated the size of their hand, selecting photos showing hands 8% smaller compared to healthy subjects (99.8% of the real hand dimension in patients vs. to 107.8% in healthy controls). Although the MIRAGE system used in this last study induced a visual illusion correcting the distortion evaluated at the baseline, we considered this study only as an evaluation study because the authors did not provide pain measure, nor disability questionnaire as outcome measure (see **Table 2** for exclusion criteria).

Self-administered questionnaire

Fremantle back and knee awareness questionnaire Seven studies were conducted adopting the FreBAQ validated by Wand et al. (2014, 2016) on CLBP patients (Janssens et al., 2017; Ehrenbrusthoff et al., 2018; Nishigami et al., 2018), in post-partum (Beales et al., 2016) or pregnancy-related pelvic pain (Wand et al., 2017), and knee osteoarthritis (Nishigami et al., 2017). Three studies are psychometric validations of the FreBAQ in other languages (Janssens et al., 2017; Ehrenbrusthoff et al., 2018; Nishigami et al., 2018). Fifty of 51 patients with CLBP (98%) reported some level of misperception, and only one patient recorded zero points (corresponding to no misperceptions). The mean score ranged between 8.8 (Ehrenbrusthoff et al., 2018) and 11.7 (Nishigami et al., 2018) in patients, and 0.5 to 3.3 points in healthy controls (Wand et al., 2014; Janssens et al., 2017; Ehrenbrusthoff et al., 2018) on a 0–36 scale where higher scoring indicating larger number of misperceptions. Ehrenbrusthoff et al. (2018) also reported a significant ($p < 0.01$) mean difference between patients and controls in German population adjusted for age, gender and body mass index (5.4 points; 95% CI = 3.0–7.8). However, this was lower than that found by Wand et al. (2014) of 11 points ($p < 0.001$). In all included studies investigating CLBP there was a significant correlation between FreBAQ score with, pain (intensity, duration or interference) (Wand et al., 2014, 2016; Janssens et al., 2017; Ehrenbrusthoff et al., 2018; Nishigami et al., 2018) and disability (Wand et al., 2014, 2016; Ehrenbrusthoff et al., 2018; Nishigami et al., 2018). Janssens et al. (2017) found also a difference between patients at different level of disability: the sub-group with higher disability (Oswestry Disability Index ≥20%) scored significantly higher ($p = 0.005$) than lower-disability group (13 ± 8 vs. 8 ± 6 points).

Beales et al. (2016) administered the FreBAQ to women with lumbo-pelvic pain (LPP) raised minimum 3 months post-partum, and found significantly ($p = 0.02$) more disturbances in explicit SoP in the moderate disability sub-groups of patients (median score: 8/36 points) than in pain free controls (median score: 2/36 points). They also found more perceptual dysfunctions in moderate-disability sub-groups respect to low-disability patients (median score: 6.5/36 points) and pain free controls (median score: 2/36 points), however there was no statistical significance (respectively, $p = 0.282$ and $p = 0.095$; *personal communication)*. Wand et al. (2017) instead collected data on pregnancy-related LPP (within the 3rd trimester of pregnancy and not over the 38th week): women with pain referred significantly ($p = 0.005$) more perceptual dysfunctions than those pain-free (median score: 3.5/36 vs. 1/36), and authors found a significant correlation ($p = 0.027$) of FreBAQ score with pain intensity ($r = 0.378$), despite it was not correlated with self-reported disability ($p = 0.143$).

Finally, Nishigami et al. (2017) adopted the FreBAQ for knee osteoarthritis patients, validating the FreKAQ. They found significantly ($p = 0.001$) more perceptual dysfunctions in patients than in controls (median difference: 9 points), and a significant correlation ($p < 0.002$) between pain in motion (*rho* = 0.37*)* and disability (*rho* = −0.41), but not with pain duration (rho = −0.06, $p = 0.76$).

Neglect-like symptoms questionnaire Two studies using the NLSQ developed by Galer and Jensen (1999) and Frettlöh et al. (2006) in CRPS. The NLSQ measures the cognitive and motor neglect, with higher scoring indicating more neglect referred symptoms. Hirakawa et al. (2014) found that 36% of patients with knee osteoarthritis scored more than 100 on a 0–500 range three weeks after arthroplasty, decreasing at 19% at six weeks (p-value not reported). The mean NLSQ score decreased from 77.7 to 42.2 points (p-value not reported); however, the standard deviation was high due to a large inter-subject variation. The motor neglect sub-scale (MNss) was associated in multiple regression analysis with pain both at 3 ($\beta = 0.50$; $p < 0.01$) and 6 weeks ($\beta = 0.53$; $p < 0.01$), where β represents points on MNss per unit of pain intensity, and with the improvement of range of motion at 6 weeks ($\beta = -0.28$; $p < 0.01$), with β describing changes in MNss score per range of motion degrees. Magni et al. (2018) reported a presence of neglect-like symptoms in hand osteoarthritis more often than in control healthy subjects ($p < 0.001$)(prevalence rate not reported); however, the magnitude of the difference was very low (median difference = 0.5 points; *personal communication*).

Body Ownership

The study of Martínez et al. (2018) is the only one to analyse body ownership through the RHI paradigm. They found that fibromyalgic patients were more susceptible to experience the illusion compared to healthy controls, scoring significantly ($p < 0.05$) higher both in proprioceptive drift sub-scale and in 4 out 5 items of the agency scale.

Perception of Surrounding Space

No studies assessed the personal and peri-personal space in MDRDs. Three studies investigated perception of extra-personal space using the Computerized Rod And Frame test (CRAF) in (Docherty et al., 2012; Treleaven and Takasaki, 2015) acute/recurrent and CNP (Grod and Diakow, 2002). During the CRAF subjects were asked to set a rod to the true vertical or horizontal: it provided a measure of the absolute error for the subjective perception of visual verticality/horizontality (SVV—SVO), and assessed the dependence on visual input for spatial orientation. Treleaven and Takasaki (2015) found a significant difference ($p < 0.05$) between patients with idiopathic CNP and both whiplash affected patients for SVV error (mean difference: 0.37°), and healthy controls (mean difference: 0.5°). This difference was referred to the Variable Error (VE), indicating the variability of the performance. Also the Root Mean Square Error (RMSE), representing the overall accuracy in achieving the true vertical, resulted significantly different ($p = 0.01$) between idiopathic neck pain patients and the other two groups (mean difference: 0.51° respect to healthy controls, and 0.58° respect to whiplash patients. By contrast, the absolute error and the direction of error were not able to detect between-groups differences (p-values respectively of 0.99 and 0.6). Unexpectedly, difference between patients with Whiplash Associated Disorders (WAD) and healthy controls was not significant in all error measurements evaluated, despite a higher level of disability in this sub-group respect to that with idiopathic neck pain. Docherty et al. (2012) (Docherty et al., 2012) assessed the (SVH error) in addition to the SVV error. Although both parameters were significantly different ($p < 0.05$) between CNP patients and healthy controls, they nevertheless fell into the range considered normal (<0.5°). A significant greater error ($p < 0.001$) in patients than in healthy controls was also found when using a variant with the frame tilted clockwise or counter-clockwise by 18°, but even in this case the median difference was small (<2°). Notably, 16% of patients with CNP scored higher than normal error in both the SVV and SVO, and they reported significantly ($p < 0.016$) higher disability at the Neck Disability Index respect to other patients with errors falling within the reference range of normality. The same small difference between groups (mean difference = 1.99°; $p < 0.001$) in SVV was found by (Grod and Diakow, 2002): in this case the experimental group was constituted by acute or recurrent neck pain, instead of CNP.

Qualitative Studies

From the interviews administered by Lauche et al. (2012a) emerged a distorted subjective perception of neck proportion (as if it was swollen) in CNP patients persisting even when patients were aware that this perception did not match actual appearance. The perception of enlarged body parts was found also by Valenzuela-Moguillansky (2013) in fibromyalgic patients through the administration of 'elicitation interviews', a methodology stemming from the phenomenological approach. They also reported other modification of the explicit SoP as changes in perceived heaviness, thickness and ownership: in stages of elevated level of pain, some patients described a paradoxical experience as if the painful body parts did not belong to them. Finally, they referred also the inability to localize painful body parts and an associated narrowing of the near space, as if it was shrunk while the body became larger.

Intervention Studies

Four out twelve intervention studies were conducted in an experimental setting (Preston and Newport, 2011; Diers et al., 2013; Stanton et al., 2018; Nishigami et al., 2019), while the remaining eight were conducted in clinical settings (Barker et al., 2008; Wand et al., 2011, 2013a; Morone et al., 2012; Paolucci et al., 2012; Vetrano et al., 2013; Ryan et al., 2014; Louw et al., 2017). **Supplementary Table 6** in Additional materials reports the methodology applied in each study, the clinical characteristics of patients, the outcome measures, the follow-up periods, and results. Only three studies monitored the treatment effect at follow-up periods (Wand et al., 2011; Morone et al., 2012; Vetrano et al., 2013). The study of Gilpin et al. (2015), despite adopting an intervention tool (the MIRAGE system), was excluded from the intervention studies because it lacked an end-point that measured pain and/or disability, thus it was assessed only under the evaluation studies for baseline data reported the perceived distortion of osteoarthritis patients' hand. One study (Diers et al., 2013), adopted the term 'upper back pain' with no details about the definition and boundaries of the functional diagnosis: first author declared to have enrolled patients with CNP (*personal communication).*

Tactile Localization Training

Three studies (Barker et al., 2008; Wand et al., 2013a; Louw et al., 2017) adopted the concept of the somatic localization of touch (Longo et al., 2010), as a trainable perceptual ability. Wand et al. (2013a), in their cross-over randomized trial, administered a single session of acupuncture on the low back of two groups of 25 CLBP patients, asking in one group to localize where the needles have been inserted by depicting the point of needle insertion on a body chart. Pain was significantly ($p = 0.008$) less post-treatment (11-Numeric Rating Scale—NRS: −0.9; 95% CI = −0.3 to −1.5), regardless of the order of treatment administration ($p = 0.182$), but the magnitude of change was not clinically relevant. Pain reduction was higher ($p = 0.011$) for the group where the acupuncture was associated with the sensory discrimination training, however the effect size was not clinically relevant (11-Numeric Rating Scale: −0.8; 95% CI = −1.4 to −0.3). Louw et al. (2017) described a series of sixteen CLBP patients on which they administered a single, 5-min session of tactile localization, measuring pain intensity (11-NRS) and functionality (active lumbar flexion in centimetres). Patients were touched with the back of a pen on nine zones of the lower back in a random order; they were asked to localize the stimuli on a corresponding 9-block grid. Immediately after the treatment, pain decreased by 1.9 points (range: 0–6), and lumbar flexion increased of 4.8 centimetres (range: −1 to 21), in both cases over the clinical significance. Barker et al. (2008) compared the effect of a device (the FairMed) that is based on the principle of the localisation task, with a conventional TENS. The FairMed contains 16 vibrating points, controlled at distance and randomly activated. The subject has to localise where the vibrating point is acting and the device signals the correct responses through a visual and auditory feedback. Pain and disability improved significantly ($p = 0.05$), but without significant difference between the two devices.

Combined Therapy

Three studies (Morone et al., 2012; Paolucci et al., 2012; Vetrano et al., 2013) adopted the "SuPeR" (Surface for Perceptive Rehabilitation tool) and other two used a gradual perceptual re-training program (Wand et al., 2011; Ryan et al., 2014); all studies enrolled CLBP patients. The SuPeR treatment provided the adoption of postures and the execution of active exercises while lying supine on a table with a series of deformable latex cones of different hardness having the goal of stimulating the trunk skin surface: patients were asked to count and localize tactile stimuli, or to discriminate the hardness of cones. Morone et al. (2012) found an effectiveness in pain and disability levels reduction both for SuPeR treatment and Back School program respect to control group (medical and pharmacological assistance only) post-treatment and after 24 weeks ($p < 0.001$), but differences between two groups, despite statistically significant ($p < 0.001$), were never clinically relevant. The same trend was found also by Paolucci et al. (2012). Vetrano et al. (2013) studied a variant of the SuPeR treatment against the standard procedure described by Morone et al. (2012). The efficacy of the two proposed version of the SuPeR treatment were substantially equal ($p > 0.05$), and both procedures improves pain and disability respect to baseline values ($p < 0.001$), with variable clinical relevance (11-VAS range: −2 to −5.5, Oswestry Disability Index range: −14 to −21). Although an improvement in pain level and disability was globally reported for SuPeR approach, the effect size was variable and not always clinically significant at follow-up periods. Wand et al. (2011) described three cases of patients with CLBP treated with a mixed treatment comprising education, graded perceptual training (localization and graphesthesia tasks) and graded motor retraining for a minimum of 10 weeks: pain decreased at the end of treatment and after 1 month (2.9 and 3.9 on 11-NRS), as well as disability (5.2–9.6 on the Roland and Morris Disability Questionnaire-RMDQ), with statistical significance ($p < 0.001$). Finally, Ryan et al. (2014) adopted in a pilot-randomized trial controlled with a placebo group, the graded perceptual re-training protocol described by Wand et al. (2011), in adjunct to usual physiotherapy cares. Pain and disability improved after treatment in experimental group (−8 on 101-VAS and −1.6 on RMDQ), but without statistical significance ($p>0.05$), respect to placebo group (−33.2 on 101-VAS and −4 on RMDQ; $p < 0.0$).

Experimental Setting

Among studies conducted in experimental settings, Diers et al. (2013) tested the visual manipulation of the neck in CNP patients and healthy subjects Authors provided visual feedback, of the neck (neutral, enlarged or downscaled visual appearance) and of a neutral body part (hand dorsum), during pressure and electrical pain stimulation of the trapezius muscle. They found that all visual conditions of the neck ($p < 0.001$) but not of the neutral hand ($p>0.05$), reduced the perceived intensity of applied acute painful stimuli, both in patients and in controls, but changes were all under the clinical significance. Preston and Newport (2011) adopted the MIRAGE-multisensory illusion system, in patients with hand osteoarthritis, while Stanton et al. (2018) applied it in knee osteoarthritis patients. The MIRAGE system involved the visuo-tactile manipulation of a body part, inducing their stretching or a shrinking visual appearance, in addition to a tactile stimulation applied by the examiner that may be directed in a congruent or incongruent modality (tactile stimulation in the same direction of the visual illusion (e.g., in stretching direction, or in the opposite way). Both studies reported an analgesic effect, with a reduction in pain varying between 45 and 50% respect to the baseline in the study of Preston and Newport (2011), and 25% in the study of Stanton et al. (2018). In this last study it was also found that repetition of the illusion, better than prolonging the exposure, produced additional pain relief (40% respect to the baseline). Finally, Nishigami et al. (2019) adapted and preliminary tested the MIRAGE system in two CLBP patients without the adjunct of the tactile stimulation to the visual manipulation. In this pilot-study, the authors proposed a visual manipulation of the trunk modifying its muscular appearance, based on the common maladaptive beliefs of CLBP subjects about robustness and perceived vulnerability of their back. This kind of "cognitive" illusion seems to reduce pain only in the subject A, having higher level of body perception dysfunction (FreBAQ score: 29/36), catastrophization (Pain Catastrophizing Scale score—PCS: 50/52) and maladaptive beliefs (Back Beliefs Questionnaire score—BBQ: 67/45), respect to the subject B with lower scoring on these outcomes (FreBAQ: 0/36; BBQ: 39/45; PCS: 8/52).

Qualitative Studies

The study of Lauche et al. (2012a) is a qualitative investigation embedded in a RCT on the effect of the cupping therapy in CNP patients, compared to similar patients on a waiting list to receive treatment (Lauche et al., 2012b). From the interviews emerged a subjectively referred reduction in neck size (smaller), as consequences of pain relief. The Body Image Drawing (BID) appeared changed in both groups, but drawings were more complete and lines more symmetric, in the cupping therapy group.

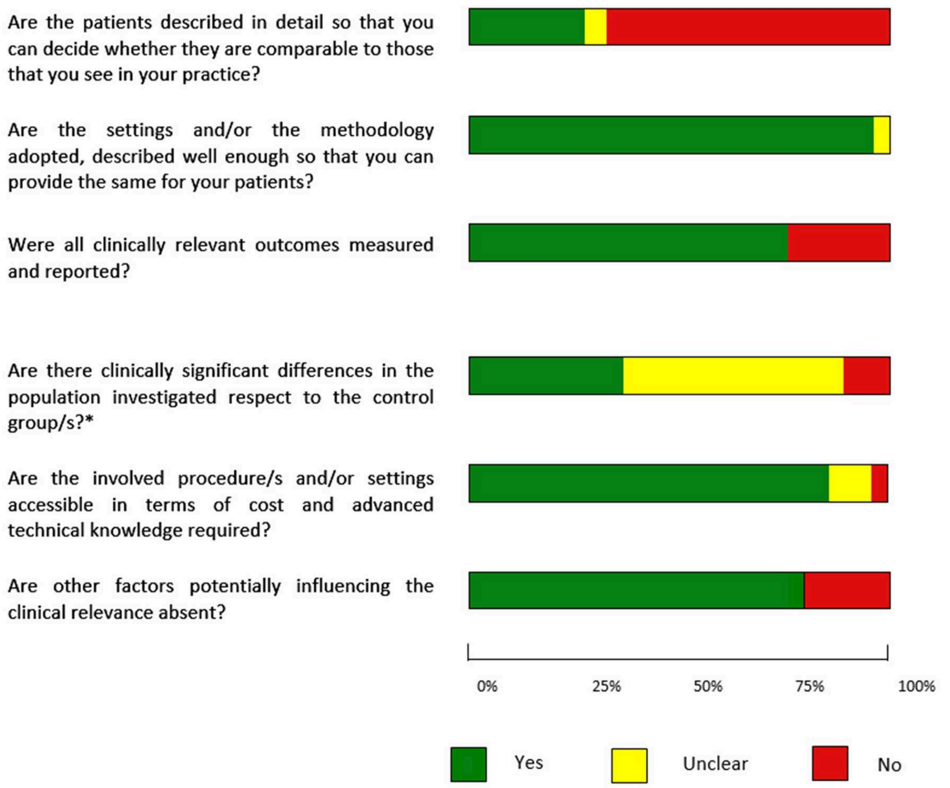
Methodological Considerations

Only 5 out of the 38 included studies (Barker et al., 2008; Wand et al., 2013a, 2016; Adamczyk et al., 2018b; Nishigami et al., 2018) provided a-prori calculations of the sample size, thus their results cannot be generalized to larger population. A rich variety of research designs was adopted: 9 out 38 studies were case studies, case series, pilot trials or preliminary investigations (aggregated they represent 24% of all included studies) (Moseley, 2008; Preston and Newport, 2011; Wand et al., 2011; Louw et al., 2017; Moreira et al., 2017; Adamczyk et al., 2018a,b; Stanton et al., 2018; Nishigami et al., 2019) This strongly limit the comparison of findings between studies. These nine studies had also small sample sizes ranging between 2 and 20 subjects in nine studies (24% of cases), limiting the generalizability of results. Inclusion and exclusion criteria have been poorly documented in 29/38 studies (76%) (**Figures 7**, **8**): the selection of the target population may have been not adequately performed, potentially biasing the validity of results. Sixteen percent of all included studies were conducted in an experimental setting (Grod and Diakow, 2002; Wand et al., 2010; Docherty et al., 2012; Gilpin et al., 2015; Treleaven and Takasaki, 2015; Martínez et al., 2018), limiting the applicability of methodologies proposed in clinical practice.

Assessment Studies

Groups of control subjects were not tested in six studies (Wand et al., 2013a, 2016; Hirakawa et al., 2014; Adamczyk et al., 2018a,b; Nishigami et al., 2018), and two case-control investigations had no healthy subjects comparisons (Moseley, 2008; Beales et al., 2016): this issue represents a major limitation of these works, potentially limiting the validity of their findings. Although we can presume that explicit SoP of body parts should be normal in unaffected people (Longo and Haggard, 2012), a degree of distortion for implicit SoP has been found even in healthy people (Fuentes et al., 2013; Longo, 2017). For this reason the absence, or small size of healthy control groups weighs more on the validity of the studies investigated the implicit SoP (Wand et al., 2010, 2013b; Adamczyk et al., 2018a,b) respect to those investigated the explicit SoP.

The FreBAQ and FreKAQ questionnaires were adapted from the NLSQ of Galer and Jensen (1999) and Frettlöh et al. (2006) validated in CRPS patients. Studies adopting these outcomes represented the majority of all the assessment studies (40%). It should be noted that questionnaires measuring explicit SoP are not validated against standard measures of reference. Of course, the criterion-validity of scales measuring this construct remain unknown and the contribution of the implicit body model and of the explicit cognitive representation are difficult to disentangle. Nevertheless, it must be considered that FreBAQ and FreKAQ involve two items asking for the explicit size and shape perception of body parts (items 6–9): they could be validated adopting recently proposed objective measure for the explicit SoP itself and for the body model (Longo and Haggard, 2010; Fuentes et al., 2013; Spitoni et al., 2015; Adamczyk et al., 2018b), accounting for



*If control groups are absent: is there a correlation of the dysfunction detected with at least one out the two clinical variables of pain and disability?

Adapted from: Furlan AD, Pennick V, Bombardier C, van Tulder M, Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine. 2009 Aug 15; 34(18):1929–41.

FIGURE 7 | Summary of the evaluation for clinical relevance of included assessment studies.

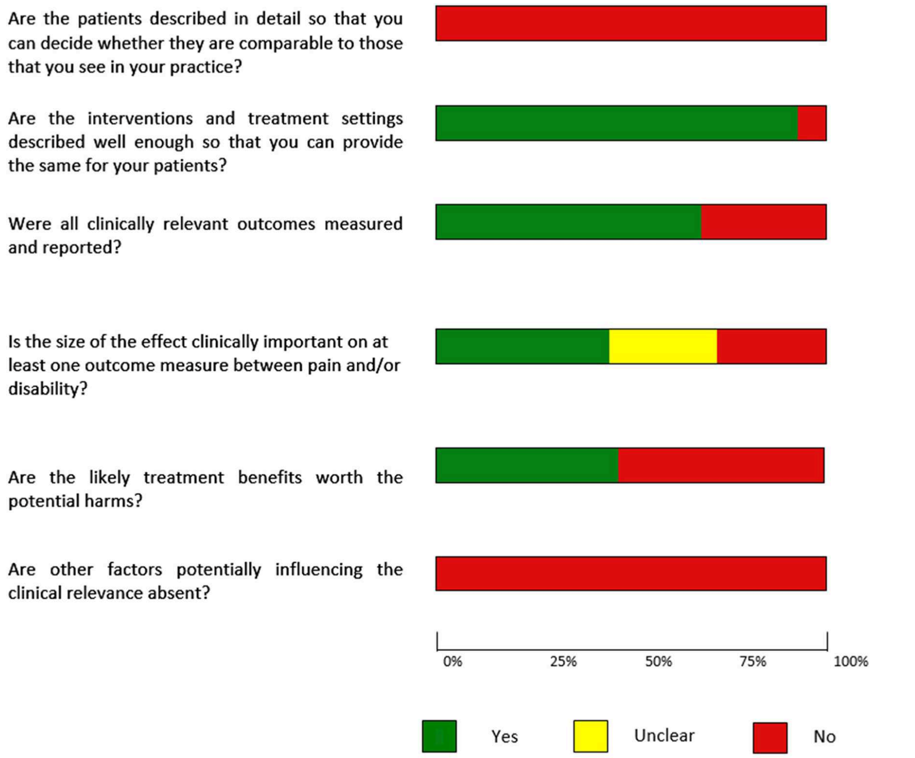
the implicit perception of metric sizes of body parts. Moreover, item 5 of FreBAQ/FreKAQ asked about the explicit perceived location of body parts in space: it may be validated adopting the objective methodologies proposed by Longo and Haggard (2010) for the implicit position sense. Finally, other items investigated the body ownership (item 1) and agency (items 3 and 4), two constructs that have been extensively studied through the RHI paradigm and relative psychometric measures (Longo et al., 2008a).

Notably, we found only one study investigated the responsiveness of assessment tools respect to changes in clinical status (Lauche et al., 2012a). However, the qualitative nature of this investigation provide us only indicative data.

Treatment Studies

As highlighted in **Figure 8**, some issues threatened the clinical relevance of included studies. Four studies recruited not adequate control groups: for e.g., the study of Barker et al. (2008) compared the FairMed device with the TENS in CLBP patients. However, Cochrane Reviews (Khadilkar et al., 2005, 2008) found limited evidence for the use of TENS in CLBP treatment, and the international guidelines recommend to use a mixed-type of intervention in patients with this kind of disorder, composed by physiotherapy, exercises and psychological treatments (National Guideline Centre, 2016). Thus, the sole use of the TENS cannot be considered as the gold standard treatment for LBP, and FairMed device should be tested against a placebo-control group or with another more effective treatment. The same issue involved also the study of Morone et al. (2012), Paolucci et al. (2012), and Vetrano et al. (2013) in which the experimental SuPeR treatment approach for CLBP was compared to a group of patients who performed back school exercises, and to another group who performed a variant of the standard SuPeR treatment. The qualitative study of Lauche et al. (2012a) was embedded in a RCT (Lauche et al., 2012b) with a waiting-list control group and therefore it lacks of a comparison with other usual cares or placebo interventions.

Only two studies (Stanton et al., 2018; Nishigami et al., 2019) evaluated at the baseline the presence of perceptual dysfunction thus, a large part of the treatments provided perceptual tasks aimed to reduce pain and/or disability without taking in consideration the potential relationship between SoP



Adapted from: Furlan AD, Pennick V, Bombardier C, van Tulder M, Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine. 2009 Aug 15; 34(18):1929–41.

FIGURE 8 | Summary of the evaluation for clinical relevance of included treatment studies.

and pain perception. This methodological issue represents a major limitation of all intervention studies. Failure to detect possible sub-groups, as those found in some assessment studies for explicit SoP (Mibu et al., 2015; Nishigami et al., 2015; Moreira et al., 2017), may have limited the effectiveness of therapeutic procedures because authors may not have taken into account that different kind of misperception could produce variable results to the same treatment. Currently, therefore, it is not possible to draw any conclusions regarding their potential clinical value.

The adverse events were not reported across all included studies (**Figure 8**): although the majority of studies adopted non-invasive procedures we lack evidence about the occurrence of side effects, especially for two studies using invasive procedures (acupuncture and cupping therapy) (Lauche et al., 2012a; Wand et al., 2013a). Moreover, authors of the studies where bodily illusions were administered through mediated-reality systems (Preston and Newport, 2011; Diers et al., 2013; Stanton et al., 2018; Nishigami et al., 2019), despite the minimal invasiveness of the procedures, did not report information for the tolerability of the equipment and of the illusions itself. In eight studies, the therapeutic procedures required dedicated technological (Barker et al., 2008; Preston and Newport, 2011; Diers et al., 2013; Stanton et al., 2018; Nishigami et al., 2019) or homebuilt equipment (Morone et al., 2012; Paolucci et al., 2012; Vetrano et al., 2013): even if the materials assembly procedure is well described (Morone et al., 2012; Paolucci et al., 2012; Vetrano et al., 2013), costs were not reported, potentially limiting the clinical applicability of these therapeutic tools. Sixty-three percent of patients in the study of Barker et al. (2008) reported faults of the FairMed device during the experiments, a concern that may have limited the efficacy of the treatment tested.

Except for Morone et al. (2012) and Vetrano et al. (2013), almost all studies provided follow-up periods no longer than 4 weeks, thus limiting the possibility to assess long terms effect for treatments proposed. From a conceptual and terminological point of view, in some studies authors reported using sensory-based interventions (Barker et al., 2008; Morone et al., 2012; Ryan et al., 2014) where, instead, perceptual-based therapeutic strategies were tested. This distinction is not trivial because primary sensory processing is different respect to higher-order mechanisms underlying SoP (Longo and Haggard, 2010; Hillier et al., 2015; Mancini et al., 2015; Spitoni et al., 2015). This terminological misuse may hide an important conceptual issue: some studies may have been conceived and designed with the goal to ameliorate primary *somatosensations* (tactile acuity, proprioception, etc.), rather than SoP, and the results found may have been consequently biased by these conceptual and practical mismatches.

Finally, calculation of effect sizes' confidence intervals were not possible in four studies (Preston and Newport, 2011; Morone et al., 2012; Vetrano et al., 2013; Louw et al., 2017) due to lack of relevant information: this reporting bias may have compromised the accuracy of results.

DISCUSSION

To "live" our own body constitutes a fascinating and complex experience because the body represents a unique multisensory object. The body experience is not direct, as well as bodily illusions and pain perception, two perceptual experiences that illustrate the complexity of mental organizations. Rather, it is filtered by a numbers of factors such as somatosensory inputs, perceptual information and body memory (Riva, 2018). Therefore, to study perceptual disorders in painful conditions represents an opportunity to explore the mechanisms underlying how our brain generates the experience of one's body. The aim of this review was to provide a comprehensive map about the literature published on perceptual disorders in painful MDRDs, with the main goal to identify gaps in current knowledge and to obtain useful information for the future research agenda. Our findings should be interpreted considering the large methodological variety of included studies.

The amount of literature found (37 articles) attests that, since the first investigation of Moseley (2008), overall these topics have been received some attention during the last decade. Specific sub-groups of MDRSs have been investigated more extensively, as in the case of spinal pain. CLBP, CNP and Pelvic Pain, taken together, represent about 80% of all the included studies. At the same time, it is noticeable how some others clinical conditions such as the rheumatic diseases remained with little or sparse interest. For example, rheumatoid arthritis was not investigated, and only two studies (5%) investigated fibromyalgia (Valenzuela-Moguillansky, 2013; Martínez et al., 2018). Another poorly explored area is pain in upper and lower limbs (15% of included studies), among which osteoarthritis was the only studied condition (Preston and Newport, 2011; Hirakawa et al., 2014; Gilpin et al., 2015; Nishigami et al., 2017; Magni et al., 2018; Stanton et al., 2018).

Summary of Evidence and Clinical Interpretation

Assessment Studies

We found a wide and heterogeneous literature published in the field of MDRDs about SoP, SpP and BO. It predominantly concerned about the assessment (66% of included studies, 25/38), respect to the intervention strategies (34%, 13/38). Some preliminary evidence of distorted body experience in MDRDs emerged, mainly in the area of the explicit SoP for spinal pain assessed through the BID task (Moseley, 2008; Lauche et al., 2012a; Mibu et al., 2015; Nishigami et al., 2015; Moreira et al., 2017), questionnaires or visual estimation tasks (Gilpin et al., 2015). These preliminary findings are in line with evidence found in CRPS (Galer and Jensen, 1999; Förderreuther et al., 2004; Frettlöh et al., 2006), although with apparent less magnitude and frequency. In fact, NLS were reported in 54.4–90.2% of CRPS patients respect to 19–36%. found in MDRDs (Hirakawa et al., 2014). Notably, the results obtained through the BID are difficult to interpret and compare to each other due to the qualitative nature of this task: the assessment of the altered explicit SoP is left to the clinician's subjective judgment, potentially leaving a large margin of error in interpreting the results of the test. Moreover, both the BID task and questionnaires like FreBAQ/FreKAQ and NLSQ, involved a self-description and depiction of own's body parts in which are involved both perceptive and cognitive/affective contributions that are not easily separable. For this reason, these tasks should be considered as a complex and multidimensional way to assess explicit body experience. On the other hand, although some promising assessment methodologies have been proposed, a substantial gap in knowledge exists in the area of the implicit mechanisms guiding perceptual abilities, like the estimation of body parts' size and its location in space. The absence of studies that investigate the sub-domain of the implicit SoP may be interpreted as a lack of appropriate tools in MDRDs able to investigate this construct, or as a sparse knowledge about the distinction between implicit and explicit mechanisms underlying SoP. This may be not surprising if we consider that: a) this area of investigation is peculiar of the neuropsychology rather than rehabilitation sciences dealing with MDRDs; and (a) the comprehension about neural and operational mechanisms of body experience has grown only in the last few years (Longo et al., 2008b, 2015; Longo, 2015; Gallace and Bellan, 2018).

We found only three studies investigating the implicit SoP in MDRDs (Wand et al., 2013b; Adamczyk et al., 2018a,b), of which one is a preliminary validation study and another is a case-study. Therefore, it appears that implicit SoP in MDRDs has received little attention, as well as in CRPS, where only sparse studies have been investigated this sub-domain of body perception (Lewis et al., 2010b; Reiswich et al., 2012). Despite this, some methodologies proposed in preliminary studies showed good psychometric values, as in the case of the 2-PET (Adamczyk et al., 2018b), and are easy to be implemented both in clinical practice (Wand et al., 2013b; Adamczyk et al., 2018a) and in future research studies.

Variable results were found for the association of SoP disorders with pain intensity, duration and disability. Higher and stronger associations were found in studies that examined the explicit SoP (mainly those adopting the FreBAQ and FreKAQ) compared to other methodologies, while conflicting results were found for studies assessing the implicit SoP. However, in this last case, the small number of studies (Wand et al., 2013b; Adamczyk et al., 2018a,b) and of subjects recruited may have influenced the findings. Overall, it is not possible to draw conclusions about causation due to the lack of cohort studies. In fact only one study had a longitudinal research design (Hirakawa et al., 2014): authors found a decreased level of perceptual dysfunctions 6 weeks post-knee arthroplasty but standard deviation values were high, indicating large variation among patients. Thus, it is unclear whether SoP dysfunctions are a consequence of persistent painful states, potential contributing factors or an epiphenomenon of pain. One proposed hypothesis has been reported in pregnancy-related pelvic pain in which body changes precede the onset of pain: in this case, anatomical variations in body sizes may have caused pain-related thoughts and fear of movements, generating maladaptive behaviours and altered body perceptions (Beales et al., 2016). In other conditions different than pregnancy-related ones, this combination of factors may explain misperceptions occurring only in body parts potentially affected by increment of size (e.g., axial joints, interphalangeal and metacarpal joints) where SoP distortions could occur subsequently to swelling phases (McCabe et al., 2004), but they may be not able to explain misperceptions affecting the spine.

Sub-groups detection

In some studies (Mibu et al., 2015; Nishigami et al., 2015; Moreira et al., 2017) seem to emerge sub-groups of patients with different features for the explicit SoP (normal, augmented and shrunken), although the association of each group with higher disability levels, or pain duration and intensity remains unclear. Similarly, for implicit SoP, Adamczyk et al. (2018a) presented a two-case report in which one patients showed an overestimation of the painful low-back side compared to non-painful locations in 2-PET (range: 45–206%) and an opposite trend in the second subject (underestimation ranged between 12 and 22%). However, it cannot be established if two or more different sub-groups emerged also for the implicit domain of SoP because this is the only study that found this apparent trend. The same authors, in another study with larger sample of CLBP patients (Adamczyk et al., 2018b), were not able to find the same sub-groups split found in the first double-case study. They also identified an overall underestimation of both sides of the spine in 2PET, challenging the relationship between pain location and body perception distortion.

Body ownership

As a part of our body experience, we have to consider that mental representations of own body include the concept of shape and contours perception of body parts (James, 1890) and the boundaries between them and the external space. The plasticity of this kind of body *representation* has been extensively studied through the RHI paradigm (Botvinick and Cohen, 1998). However, we found only one study investigating the response to the RHI in MDRDs (Martínez et al., 2018). These authors found that fibromyalgic patients were more prone to experience the illusion than controls. The capacity to localize and confine body sensations within the corporeal boundaries requires an intact *somatorepresentation*: a misperception in which a rubber hand 'taking the place' of own's real hand (body representation instability), could indicate a dysfunction in multisensory integration underlying SoP function, but it is not clear the relationship with clinical relevant variables, and thus the potential role played in pathophysiology of chronic pain. To the best of our knowledge, only one study was published assessing the RHI in CRPS patients (Reinersmann et al., 2013). Authors found preserved multisensory integration despite the presence of neglect-like symptoms, indicating a possible dissociation between the mechanisms involved in BO and explicit SoP. Noteworthy, it seems to appear a potential analogy between fibromyalgia and eating disorders: both conditions seem to have a more instable BO respect to healthy controls (Mussap and Salton, 2006; Eshkevari et al., 2012; Keizer et al., 2014) and are joined by augmented vigilance to internal body signals. In addition, they seemed to show dissatisfaction regarding some body parts, those more painful in fibromyalgic subjects and emotional-sensitive ones in anorectic and bulimic patients. Body dissatisfaction is thought to be caused by the discrepancy between an ideal body model and the current self-perception (Strauman et al., 1991; Vartanian, 2012). Despite the causation relationship is still unclear, it was found a correlation between negative body affective perception and pain severity in fibromyalgic patients (Akkaya et al., 2012). In our opinion, in order to avoid ineffective and limited approaches, as already found in eating disorders (Eshkevari et al., 2014), it should not be neglected the presence of such negative body-cognition appraisal also in fibromyalgic patients. The variable contribution to body experience of cognitive, affective and perceptual mechanisms should be considered in further studies, as already proposed for eating disorders treatment (Riva, 2011; Keizer et al., 2014; Serino et al., 2016a,b).

Space perception

Evidence emerged across included studies seemed to highlight the absence of SpP dysfunctions, at least for the extra-personal space measured through the CRAF test in a sample of patients with CNP and WAD: errors in SSV and SVO were under the limit of normality or very modest, and were not correlated with disability. The lack of studies conducted in disorders different than CNP and WAD makes it difficult to extent these findings to others MDRDs, or to compare these results with those found in CRPS (Sumitani et al., 2007a,b; Uematsu et al., 2009; Reinersmann et al., 2012; Christophe et al., 2016).

Treatment Studies

The majority of published intervention studies were preliminary pilot-tests, case studies and case series, or were conducted in experimental settings. For these reasons, evidence emerged about the intervention strategies proposed are very limited. Moreover, it is difficult to estimate the relative effectiveness of each single therapeutic component for studies adopting concomitant multiple approaches (Wand et al., 2011; Morone et al., 2012; Paolucci et al., 2012; Vetrano et al., 2013; Ryan et al., 2014). Overall, intervention studies suffered the absence of preliminary assessment for dysfunctions of SoP and BO at the baseline: this issue may have limited the effectiveness of the treatments because they were not appropriately focused on specific sub-groups of patients. In fact, as shown by assessment studies, some patients with MDRDs seem to present explicit or implicit SoP disorders respect to others (Mibu et al., 2015; Nishigami et al., 2015; Moreira et al., 2017; Adamczyk et al., 2018a).

Although they must be considered within the limits of their low evidence value, case studies and preliminary investigations showed promising results of dedicated interventions (Stanton et al., 2018; Nishigami et al., 2019) addressing specific kind of SoP disorders at the baseline, as found in CRPS (Lewis et al., 2019).

Despite the presence of major methodological limitations, some therapeutic strategies could be of potential clinical value, especially in light of the brief duration and frequency of administration (Wand et al., 2013a; Louw et al., 2017).

Clinical Implications

Currently, evidence is fragmented and insufficient to guide precise assessment and intervention actions in routinely clinical practice. Nevertheless, the majority of treatment methodologies and assessment tools described in this review represent simple, safe and inexpensive procedures, feasible for the use in daily clinical practice. Some of the therapeutic approaches proposed seem to improve movement and pain without performing any physical action (Louw et al., 2017; Nishigami et al., 2019). For this reason, they may be promising strategies to use in patients with elevated pain levels and movement restrictions, as in person having high level of fear-avoidance behaviours for movements and maladaptive beliefs, especially in early rehabilitation phases (Louw et al., 2017).

Patients affected by these kind of perception disturbances (as documented in CRPS) may be reluctant, if not directly questioned (Galer and Jensen, 1999; Lewis et al., 2010a), to talk with health care providers or within the family context (Galer and Jensen, 1999), due to the bizarre features that make them appear as having some form of psychological/psychiatric disturbance (Förderreuther et al., 2004), or fearful of not being believed (Lewis et al., 2007). The perception of body contours and ownership is usually taken for granted, but in circumstances in which derangements appear between what is perceived and what is real, both pain and stressful response may potentially increase as consequence to these conditions, together with fear-avoidant behaviour. For patients, not being able to rely on information coming from their bodies and experiencing such bodily illusions can be detrimental for quality of life, social interactions and, overall, for mental health (Lewis et al., 2007; Longo, 2015). For these reasons, despite the limited diagnostic capacity of the tools now available, we believe it is important that clinicians start to approach (Geri et al., 2019) and validate this kind of unpleasant experience. For instance, clinicians could tell patients that their clinical descriptions resemble the very common situation of receiving an injection from the dentist and thereby perceiving one's lips and cheeks as uncommonly swollen and distorted, despite one's awareness that they maintain their normal size. Moving from the preliminary findings of this review, clinicians should consider the role of distorted SoP, starting from directly asking patients about their body experience, or through the administration of easy and inexpensive qualitative and quantitative tools, as the BID and the 2-PET.

Recommendation for Future Research

Despite the range of methodological issues that limit the validity of the evidence we have discussed, some of the proposed assessment methodologies and therapeutic strategies, could represent useful starting points for further research.

Considering the complexity of the body experience phenomenon, future studies should consider the concomitant assessment of different domains of bodily experience (explicit and implicit SoP, BO, and SpP), in parallel to the clinical variables commonly used for clinical studies, as some authors have started to do with CRPS patients (Lewis et al., 2019). Intervention studies should determine the response of particular sub-groups of patients, for e.g., those with enlarged or diminished body perception (Mibu et al., 2015; Moreira et al., 2017; Adamczyk et al., 2018a), to dedicated perceptual training interventions (Lewis et al., 2019). Moreover, the preliminary detection of perceptual impairments and the potential identification of particular sub-groups in clinical studies may help to identify individuals who could potentially benefit from dedicated treatments, or sub-groups that may be resistant to usual cares.

Future studies may implement new advanced technologies for clinical purposes. For e.g., diagnostic studies may implement more accurate new digital tools (Turton et al., 2013), aimed at overcoming the excessive subjectivity of the clinicians in the assessment of BID, but preserving at the same time the subjectivity of patients in expressing their own's SoP. Virtual and augmented reality represent probably the new frontier for the study of body representation finalized at therapeutic clinical use in body perception dysfunctions.

It may be interesting to explore also the neural correlates of body experience disorders through the adoption of neuroimaging methods, such as functional magnetic resonance imaging (fMRI), during perceptual tasks execution, without limiting the investigation to the functionality of the primary sensory area, as primarily performed in MDRDs field since now.

The available studies on assessment and treatment described here need to be replicated in larger and higher-methodological quality studies with appropriate control groups, in order to confirm preliminary results emerged, and to determine whether perceptual disorders represent clinical consistent findings. At the same time, we encourage the production of diagnostic case studies/case series and the publication of preliminary validation studies aimed to describe new assessment and treatment methodology in MDRDs as already made in CRPS (Sumitani et al., 2007a; Uematsu et al., 2009; Christophe et al., 2016; Solcà et al., 2018). We think that these two preliminary steps may be useful starting points before large scale data collection, as in the case of Adamczyk et al. (2018a,b).

The implicit and explicit body experience represents certainly a complex construct to define and investigate. Despite the absence of recognized gold-standard procedures to validate perceptual dysfunctions, it's noteworthy that other psychophysical tests have been proposed (Longo and Haggard, 2010; Fuentes et al., 2013) and may be implemented in MDRDs.

Finally, both the FreBAQ/FreKAQ and the NLSQ items were not directly derived from patients' self-experience dedicated studies, as those represented by the qualitative research. Moreover, these questionnaires were borrowed and adapted from studies on CRPS patients, rather than from studies investigating directly MDRDs patients. For these reasons, qualitative interviews-based studies may represent a useful and appropriate methodological approach to obtain relevant themes to adopt for the implementation of questionnaire items directly based on patients' "first-person" perspective (Lewis et al., 2007; Valenzuela-Moguillansky, 2013). We must consider that SoP, SpP and BO, are essentially subjective phenomena. Therefore, we cannot achieve comprehensive and deeper knowledge on this personal experience without a direct involvement of patients with dysfunctional body experiences.

Strengths and Limitations

Our research team was multidisciplinary and multiprofessional in its composition aimed at limiting potential conflicting interpretations of terminology and concepts investigated (Anderson et al., 2008). Despite the comprehensive nature of this review and the amount of sources scanned, it is possible that the limitation of our search only to English language studies may have influenced the nature of the evidence found. In order to limit this potential publication bias, we have reported in additional materials (**Supplementary Table 7**) all potential eligible studies found in other languages, having at least the abstract in English. The presence of only one author for data extraction may have been a potential source of bias: to overcome this limitation we provide a secondary data check by a second reviewer. We limited our investigation to patients >16 years old, however potentially interesting findings and assessment strategies may be found in the research area of the idiopathic scoliosis (Picelli et al., 2016; Paolucci et al., 2017). The extensive heterogeneity of included studies prevents to draw robust conclusions for clinical practice. Nevertheless, the inclusion of quantitative, qualitative and mixed-method studies at this first literature mapping stage allowed to consider the different aspects involved in the complex phenomenon of the body experience. Finally, the theme of SoP is broad and this review cannot be considered exhaustive. We excluded studies investigating the perception of own's body under dynamic condition (Valenzuela-Moguillansky et al., 2017) and the related therapeutic strategies proposed (Horwitz et al., 2003, 2004; Wand et al., 2012), because they are not considered in the theoretical framework of Longo et al. (Longo et al., 2010; Longo, 2016) that we have adopted as reference. Moreover, we did not consider other kinds of perceptual information as those related to the perceived stiffness (Haigh et al., 2003; Stanton et al., 2017).

CONCLUSIONS

Alterations of the implicit and explicit body experience have been preliminary found through this literature review. Despite the unclarity about the association or causation with chronic pain in MDRDs, perceptual dysfunctions could be reasonably considered as having a potential impact on clinical outcomes. If confirmed in future methodological robust studies, they may be potentially considered as one of the dimensions involved in clinical presentations of MDRDs, on a par with pain perception, functional limitations and restrictions in participation. Since an effective treatment depends on an effective diagnostic procedure, before conducting new treatment studies, future research should prioritize the objectification of perceptual dysfunctions subjectively referred by patients or reported through qualitative methods.

Some important questions remain open to be addressed: (a) explicit and implicit dysfunctions found in CLBP and CNP may constitute a cause, a consequence or an epiphenomenon respect to pain perception?; (b) the sub-groups highlighted in CLBP and CNP are consistently present even in other kind of MDRDs and also in the implicit domain of SoP; and (c) considering that in healthy subjects, a degree of distorted implicit somatoperception has been found in recent neuropsychological studies with respect to an intact explicit mechanism (Longo, 2017), we have to expect a further deterioration of the implicit somatoperception in those patients found to have yet an altered conscious perception of their own's body?

In order to answer to these questions, we conclude by suggesting three future research lines:

a) Longitudinal studies providing pain and multiple body perception outcome measures, along an enough large period of observation, may constitute an appropriate answer to the first point;
b) Implicit and explicit methodology of assessment should be administered in parallel to patients in order to test the potential divergences between conscious and unconscious mechanisms of body perception within and between MDRDs: this suggestion answer both to the second and the third critical points highlighted;
c) Moreover, the adoption of case-cohort studies with control groups of healthy subjects, further answer to the third point.

Overall, in consideration of the amount of literature already published since now we sustain and propose that the theoretical concept to split between implicit and explicit mechanisms of SoP may constitute an important starting point for future research agenda.

As suggested by extensive literature in neuropsychological field, pain perception appears to interact with a range of factors, among which implicit and explicit SoP, SpP and BO. For this reason, for future research agenda we encourage researchers to combine experimental lines on body experience with those studying chronic pain in MDRDs.

In consideration of findings emerged and the quality of studies found, at the state of art, the conduction of a future systematic review is appropriate only to synthesize the psychometric properties of the FreBAQ.

AUTHOR CONTRIBUTIONS

AV contributed to conception of the study, managed the database, extracted data from studies, and wrote the first draft of the manuscript. AV and DR contributed to the design and performed the first search strategy. DR and AG performed peer-review of electronic search strategies. EC, DL, and MP performed calibration phases, screening, and selection steps. DP and AV performed pilot-trials of data extraction. DP performed crosschecking of data extraction. DP and GR performed data analysis. GR, ML, and MT performed data interpretation. AG, GR, ML, and MT wrote sections of the manuscript. All authors contributed to manuscript revisions, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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