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Inter-lateral Referral of Sensation in Health and Disease Using a Mirror Illusion—A Scoping Review

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Abstract

Objective: Perception of touch is expected at the location where it is applied. However, there are indications that being touched may be perceived on the contralateral side when seen as a reflection in a mirror at midline. Such inter-lateral referral of sensation (RS) lacks evidence, as mirror therapy research usually focusses on movement-based techniques. This study aimed to map out existing research across disciplines regarding the effect of RS in health and disease, and to understand whether there is rehabilitation potential in RS.
Method: A scoping review was conducted to map out concepts and keywords across disciplines interested in this topic, using keywords in several languages, and a wide range of databases and additional sources.
Results: The review revealed mostly cross-sectional experiments and included over 486 participants: healthy, or with stroke, complex regional pain syndrome, amputation, nerve graft surgery or radial fracture. Procedures varied regarding stimulation tool, time and location, with two stimulating replacements, one the face and one a variety of areas. Response rates ranged from 0 to 100%.
In general, RS was regarded as a phenomenon or even as a predictor of maladaptive neuroplasticity. There was little research into using RS stimulation as a modulatory tool to improve sensory perception.
Conclusions: RS challenges the understanding of touch perception and elicits a range of questions regarding neuro-processing. A modulatory approach using RS has not been described, requires investigation and, if promising, development as an intervention.

Keywords: Perception/spatial processing; Cerebrovascular disease/accident and stroke; Disability/handicaps; Intersensory Processes; Mirror Therapy; Referral of Sensation

Introduction

It is expected that a healthy person perceives touch at the location where it is applied. If touch applied to the left hand, for example, is perceived on the right hand, the central nervous system of this person is not considered to be neurologically or cognitively intact, and such cases were described around one hundred years ago as “synchiria” or “allochiria” occurring in tabes dorsalis and “hysteria” (Jones, 1907, 1909; Obersteiner, 1881). Such contralateral projection is not widely expected in disease nowadays and hence not part of neurological sensory assessment (Connell, Lincoln, & Radford, 2008; Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975; Lincoln, Jackson, & Adams, 1998). All the more surprising are reports where touch sensation is referred between limbs merely by an illusion using a mirror placed at midline, reflecting the limb being

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stimulated by someone else (Ramachandran & Rogers-Ramachandran, 1996; Ramachandran, Rogers-Ramachandran, & Cobb, 1995). This phenomenon has been named "referral of sensation," "referred sensations," or "sensory referral" (Case, Pineda, & Ramachandran, 2015; Ramachandran & Rogers-Ramachandran, 1996; Sathian, 2000). To distinguish from same-side and between-person processes, it is here used as inter-lateral referral of sensation or referred sensations (RS).

In the wider context, it should not be forgotten that the healthy brain can adapt to visual distortion using mirrors, a fact that has been known in experimental psychology for a long time, because Stratton (1899) self-experimented and described mirror-induced spatial shift of the whole body position (with mirrors above and in front of the head). Erismann and Kohler developed the "Innsbruck Goggle Experiments" by turning vision upside down, showing adaptation over time (Sachse et al., 2017). A large body of literature emerged, for example, on rubber limbs and entire bodies, including neuroimaging data, suggesting body ownership to be a multisensory percept (Ehrsson, 2020; Lenggenhager, Tadi, Metzinger, & Blanke, 2007; Preston, Kuper-Smith, & Ehrsson, 2015). This current paper focuses on RS, a particular aspect of multisensory integration, that is, on the perception of touch applied to the contralateral body side and watched as a reflection in a mirror positioned between the limbs.

Sensory perceptional dysfunctions are well known, for example, as sensory loss in stroke or after nerve repair. Cortical representation of erroneous processing in connection with phantom pain has also long been demonstrated (Flor, 2003). Neuroplasticity allows the brain to recover some of the lost function following brain damage. This is well known in rehabilitation and demonstrated in a comprehensive report in 2011 by 27 U.S. experts on the (then) current evidence regarding neuroplastic changes for the benefit of clinical applications (Cramer et al., 2011). However, mirror therapy (MT) was not included at the time; using a visual illusion created by a mirror at the midline that reflects one limb superimposed on the contralateral, hidden limb. Initially described by Ramachandran over 25 years ago (Ramachandran & Altschuler, 2009; Ramachandran & Rogers-Ramachandran, 1996; Ramachandran et al., 1995), several MT protocols have subsequently been developed (Bieniok, Govers, & Dohle, 2011; Grünert-Plüss, Hufschmid, Santschi, & Grünert, 2008; McCabe, 2011; Morkisch, Thieme, & Dohle, 2019; Moseley, 2006; Rothgangel & Braun, 2013, 2014). There are a number of systematic reviews on aspects, certain medical conditions, or components of MT (Barbin, Seetha, Casillas, Paysant, & Pérennou, 2016; Boesch, Bellan, Moseley, & Stanton, 2016; Bowering et al., 2013; Ezendam, Bongers, & Jannink, 2009; Herrador Colmenero et al., 2017; Hung, Li, Yiu, & Fong, 2015; Jarrar, 2014; Mei Toh & Fong, 2012; Najiha, Alagesan, Rathod, & Paranthaman, 2015; Othman, Mani, Krishnamurthy, & Jayakaran, 2017; Rothgangel, Braun, Beurskens, Seitz, & Wade, 2011; Seidel, Kasprian, Sycha, & Auff, 2009; Thieme, Mehrholz, Pohl, Behrens, & Dohle, 2012; Thieme, Morkisch, Rietz, Dohle, & Borgetto, 2016; Thieme et al., 2018). Mirror therapy was acknowledged in an overview of Cochrane reviews of upper limb function in stroke for moderate quality evidence of benefit regarding all three components, which were upper limb function, impairment, and activities of daily living (Pollock et al., 2015). Subsequently, MT was integrated into guidance on upper limb rehabilitation poststroke (Wolf, Kwakkel, Bayley, & McDonnell, 2015).

Evidence of the effect of MT on cortical structures has been brought together by Deconinck and colleagues (2015) who included 33 studies on MT in a systematic review, using functional magnetic resonance imaging, magnetoencephalography, electroencephalography, positron emission tomography, or near-infrared spectroscopy. A total of 22 of these studies used healthy participants and five used stroke patients. A total of 11 different Brodmann Areas were listed as activated and can be grouped to three different networks: (i) attentional resources (primary and secondary visual and somatosensory areas), indicate conscious awareness of sensory feedback or control of agency, increased movement monitoring, and attentional demand and information exchange, together with visuospatial information processing and directing spatial attention; (ii) the mirror neuron system, albeit only in parts, with imitation of biological motion and acquisition of motor skills; and (iii) the motor cortex on the side of the stimulation, both in healthy people and in stroke patients. The authors confirmed that MT may be a versatile tool in movement rehabilitation as it can exert a strong modulatory influence on the system. This body of research on movement-based MT (which excluded studies on pain and tactile perception) indicates that cortical representation can be modulated with an approach using a mirror illusion.

Overall, traditional MT addresses two concepts: activation of motor abilities (stroke) and calming of pain pathways (phantom limb pain [PLP] and complex regional pain syndrome [CRPS]). All of the published protocols mentioned earlier use up to three techniques: (a) just looking at the illusion; (b) movement; and (c) handling of objects, with the latter being under discussion regarding its benefit, arguing that it distracts in the MT treatment of stroke patients. Various approaches are possible (Dohle, Altschuler, & Ramachandran, 2020). Some protocols also mention external stimulation with a brush or other textures (Grünert-Plüss et al., 2008; Rothgangel & Braun, 2013, 2014). The mention of external stimulation in these protocols implies that it is used in clinical practice, though there is no evidence evaluating its effect.

To address this gap in knowledge, a thorough literature review is required. One of the challenges of setting up such a review is that there is a multitude of disciplines interested in MT such as psychology (perception research, imaging studies), medicine (neurology, pain, and rehabilitation), allied health professions (hand therapy, neurorehabilitation and pain services, physiotherapy and occupational therapy). Therefore, unless all these areas are considered, it is likely that important area-specific keywords may be missed and concepts misinterpreted. Hence, a systematic review did not seem advisable. Instead, identification of all relevant literature was warranted to map out existing knowledge in the form of a scoping review (Arksey & O'Malley, 2005; Peters et al., 2015; Tricco et al., 2018). Therefore, the objectives of this study were (1) to explore the boundaries to similar concepts; (2) to identify relevant keywords; and (3) to identify prevalence, procedures, and tools used in RS. The population/concept/context framework (The Joanna Briggs Institute, 2015) was applied to inform the following research question: "What is known about the effect that is caused by external stimulation of a human body side on the contralateral body side when the subject watches the procedure in a parasagittal mirror"?

Methods

A pilot search using the keywords "synchiria," "touch* OR hapti* OR tactil* OR taktil*," and "mirror* OR miroir* OR spiegel* OR miroir OR specchio" preceded a full search of the literature published up to November 2020. There were no limitations regarding language or time of publication. The inclusion criteria were the following: (1) humans with and without sensory impairment; (2) stimulation of one body side using a mirror reflection that creates the illusion of the person's contralateral body side being stimulated; (3) reported perception (or lack) of sensation on the contralateral body side; and (4) simultaneous time of stimulation and expected effect. There was no restriction of language or study design in the identification stage. The protocol with the exclusion criteria was developed during the data charting and mapping process (Tricco et al., 2018) and refined after the pilot search.

Search Strategy

The following electronic databases were searched: Medline (in Ovid); Scopus (abstracts database across sciences); CENTRAL (Cochrane Library); DORIS (Database of Research Into Stroke); PEDro (Physiotherapy Evidence Database); OTseeker (Occupational Therapy Systematic Evaluation of Evidence); CINAHL (Cumulative Index to Nursing and Allied Health Literature); AMED (Allied and Complementary Medicine Database); PSYCHinfo, PSYCHarticles, and PSYCHextra (leading psychology databases); and Web of Science Core Collection. In addition, the following gray literature and PhD databases were searched: Open Grey, EThOS, BASE, OpenAire, registers of trial protocols and research communities such as ResearchGate as well as reference lists of relevantliterature. One key author was contacted regarding stimulation and answered. The initial pilot search served to identify further keywords across the specialities involved and also aimed to increase understanding of the matter among the researchers (calibration exercise, Tricco et al., 2018).

Pilot search. From the 1,353 initial hits and after removal of 209 duplicates, a sample of 228 titles (20%) were screened in parallel by AH and SJ. The initially moderate agreement rate of 57% warranted a review of both the terminology, and the inclusion/exclusion criteria, and progressed to 96% agreement in 20% of the final search. The reasons for exclusion in the pilot search were analyzed to identify and refine the selection of keywords. The hits identified as irrelevant were related to basic science (animals, medication), psychology (behavior [frontal] mirror use for self-consciousness, eyes, and emotions), medical research (cardiology, dentistry, ophthalmology, and gynecology), nursing (care), and learning and education (shape recognition). Studies that used projection onto screens seen in an ego perspective in real time were discussed and finally included, as they can be seen as a self-perspective in loco. Real-time videoing is distinct from using screens showing prerecorded stimulation as time-points differ. It is also distinct to transferral of sensation to or from other persons, which would relate to the "other" rather than the self. Keywords identified for this were "vicarious," "other person," and "another person"; all of which were terms to be excluded.

Incorporating these findings, a refined search was designed with the librarian (KN) that was consistent across databases, while remaining specific to the requirements of the individual search engines. Keywords from other languages (German, French, and Italian) were incorporated, for example, Spiegel*, miroir*, and specchi*. Further keywords identified were inter-manual, allochiria, haptic, and tactile. These search terms and their variants are shown in Table 1. Smaller databases such as DORIS, OTseeker, and PEDro were searched without exclusions, whereas searches on larger and more relevant databases, such as the psychology databases and Web of Science, were limited by excluding keywords and made more specific by adding the search term "stim*."

Search History from the CENTRAL Database

Final search. Figure 1 shows the flowchart of the final search. The refined search revealed 2,286 hits. After removal of duplicates, 1,721 titles remained. Of these, three papers were identified as corrigenda/errata and 1,718 remained. In all, 20% of the titles were screened in parallel by both reviewers, with a high agreement rate (96%). All 159 relevant abstracts were

Table 1. Search strategy

Search	Search terms	Hits
#1	synchiri* or allochiri* or allocheiri*	2
#2	hapti* or touch* or tactil* or taktil* or stimul*	70,550
#3	mirror* or spiegel* or miroir* or specchi*	2,711
#4	#2 and #3	507
#5	#1 or #4	507
#6	*other person* or vicarious* or "another person"	536
#7	dental or tooth or teeth or oral* or eye* or ophtalm* or gyn*	234,822
#8	psychiatr* or schizophren* or autism* or animal	72,521
#9	self or emotion or empathy or movement* or motion* or kinemati*	104,232
#10	letter* or shap* or writ* or rotat* or learn* or memory	78,855
#11	pharma* or medicat* or cell*	312,314
#12	monkey* or mice* or dance* or drift or environment* or development*	94,545
#13	#6 or #7 or #8 or #9 or #10 or #11 or #12	637,857
#14	#5 not #13	71
#15	sens*	105,990
#16	#14 and #15	23

Table 2. Terminology used in the included studies

Term synonymously used	Author	Alternative meaning
"sensory referral"	Case et al., 2013	Has also been used for ipsilateral referral of sensation (e.g., from cheek to phantom limb)
"referred sensations"	Hoermann et al., 2012; Peterzell et al., 2010; Takasugi et al., 2011	Ipsilateral referral of sensation (e.g., hand to cheek or genitals to foot)
"intermanual referral of sensation"	Ramachandran and Rogers-Ramachandran, 1996; Sathian, 2000	
"illusionary sensations", "perceptual illusions," and "phantom sensations"	Giummarra et al., 2010	
"mirror scratching"	Helmchen et al., 2013	
"dysynchiria"	Acerra, 2007; Krämer et al., 2008	
"synchiria testing"		Established medical definition of "synchiria" for bilateral perception of unilaterally applied touch (Tilley, 2003)
"visual experiences of unfelt touches"	Ro et al., 2004	
"dual percepts"	Hunter et al., 2003	
"illusory touch"	Wand et al., 2014	

fully screened in parallel with disagreements resolved in discussion between the researchers. Of the 33 abstracts identified as relevant, full papers were obtained where these existed, and abstract-only records were still included. Of the 33 relevant studies, 19 were excluded for the reasons given in Fig. 1. A study reporting alleviation of cramping and painful sensations as "a similar improvement occurred when the intact leg was massaged, creating the illusion of the phantom leg being massaged" gave an indication of RS (Ramachandran, Chunharas, Marcus, Furnish, & Lin, 2018), but did not have enough details to be included. Therefore, the final number of identified studies was 14, which were then grouped into 13 due to one PhD thesis containing two of the identified studies. This thesis is then reported in parts A–D, including further unpublished parts.

Quality assessment is not considered appropriate in a scoping review (Peters et al., 2015; Tricco et al., 2018), which predominantly aims to map out the existing literature. Data charting tables were designed by each of the reviewers (AH and SJ) and, following in-depth discussion, merged as agreed and presented in the following sections.

Results

Thorough reporting, highly important in psychology research (Lee & Schoenberg, 2017), was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews guideline (Tricco et al., 2018). Mapping the body of literature includes listing the keywords used by relevant authors. The range of terms is shown in Table 2.

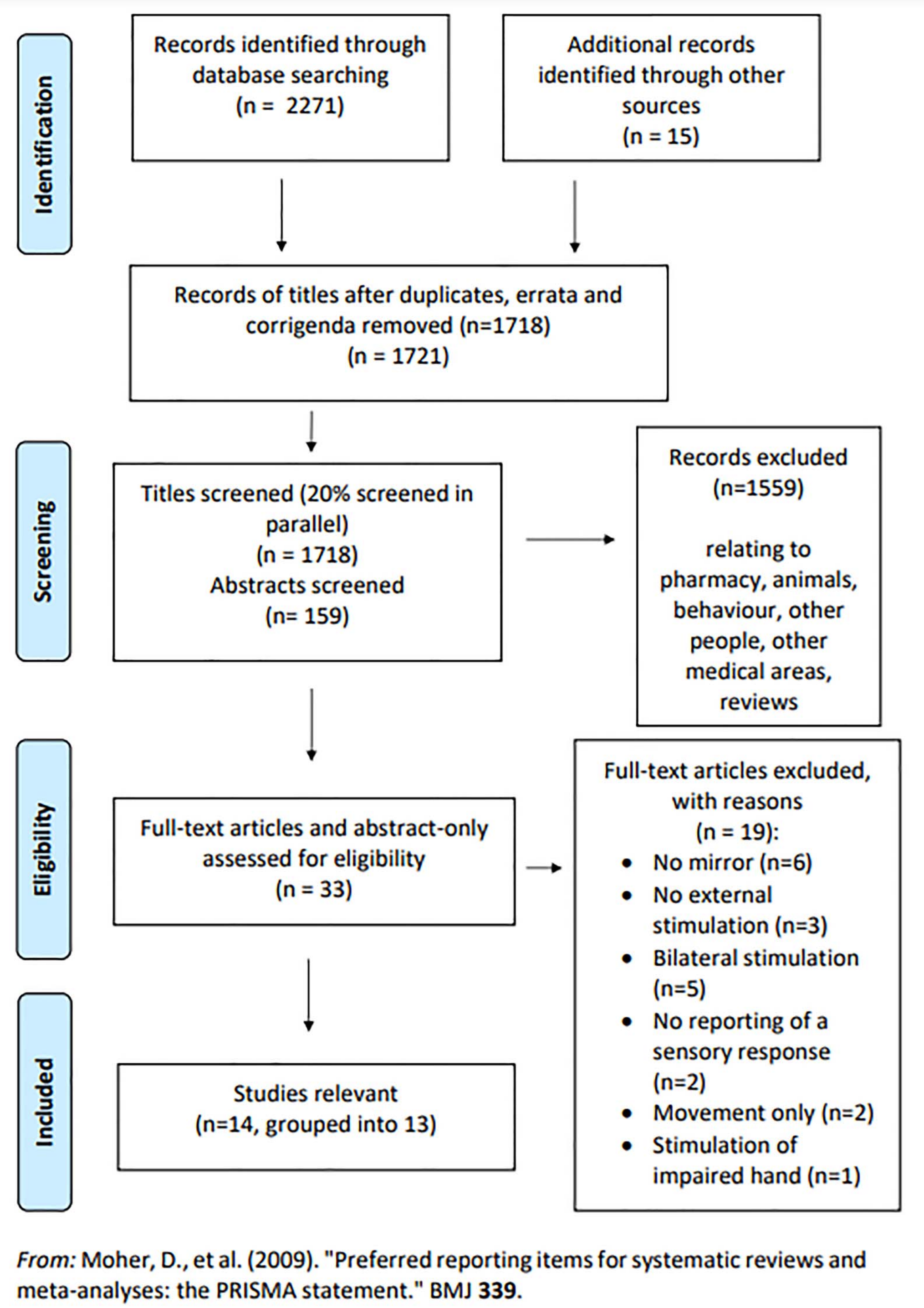

Fig. 1. PRISMA 2009 flow diagram.

"Near neighbour concepts"

During the iterative screening process, there were five categories of research identified that initially appeared relevant as they were in close proximity to the focus of this current study. The method of handling these was to collect them under the emerging headings. These were as follows:

Table 3. Included studies with categories

Health or disease	Condition	Studies
Health	Without alteration	Acerra, 2007; Giummarra et al., 2010; Hoermann et al., 2012; Ramachandran and Rogers-Ramachandran, 1996; Ro et al., 2004; Takasugi et al., 2011
	Rendered itchy	Helmchen et al., 2013
	Anesthetized	Case et al., 2013
	Replacement hand	Giummarra et al., 2010; Takasugi et al., 2011
Disease	CRPS	Acerra, 2007
	Phantom limbs	Ramachandran and Rogers-Ramachandran, 1996; Hunter et al., 2003; Giummarra et al., 2010; Peterzell et al., 2010
	Stroke	Sathian, 2000; Acerra, 2007
	Hand surgery	Wand et al., 2014
	Other pain	Acerra, 2007; Krämer et al., 2008

Note: CRPS = complex regional pain syndrome.

(1) "Without mirror": Studies evaluating synchiria without using the visual component of a mirror reflection. For example, Case, Abrams, and Ramachandra (2010) evaluated referral from a stimulated intact hand to the anesthetized contralateral hand after surgery without mirror, or to a contralateral lower limb, when the upper limb was stimulated and referral to the contralateral upper limb was already reported. Other examples of synchiria without a mirror are case reports of this phenomenon in rare presentations of synchiria in tabes dorsalis and diphtheria, and the discussions and definitions around this phenomenon (Bonato & Cutini, 2016; Jones, 1907, 1909; Obersteiner, 1881); other research evaluates the relationship between visual impairment and touch impairment (Bolognini et al., 2012);

(2) "No external stimulation": Active feeling of textures instead (Paula et al., 2016; Rosen & Lundborg, 2005); or a laser pointer study creating pain, not touch, and evaluating the effect on pain of looking at a limb in various conditions (Longo, Betti, Aglioti, & Haggard, 2009); feeling a vibrating surface (McKenzie, Poliakoff, Brown, & Lloyd, 2010). Most studies in this category used movement only without external stimulation (Metral, Gonthier, Luyat, & Guerraz, 2017);

(3) Bilateral stimulation: (Arya, Pandian, & Puri, 2018; Rosén et al., 2015; Schmalzl, Ragnö, & Ehrsson, 2013; Shan et al., 2018), or stimulation of the affected limb during MT; therefore, not creating referral between body sides (Auld, Johnston, Russo, & Moseley, 2017; Kim & Lee, 2015; Lin, Huang, Chen, Wu, & Huang, 2014), or stimulating with vibration on one side and with a light on the contralateral side (Willis, Powell, Powell, Stevens, & IEEE, 2019).

(4) "Same body side": Studies on the rubber hand illusion (RHI) that do not evaluate a reaction on the contralateral body side (usually the hand); these studies traditionally use simultaneous stimulation of a rubber hand and of the subject's own (hidden) ipsilateral hand (Botvinick & Cohen, 1998);

(5) "Another person": Studies investigating referral of touch to another person was often termed "mirror-touch synaesthesia" and can be allocated to the above-mentioned vicarious research (Banissy et al., 2009; Botan, Bowling, Banissy, Critchley, & Ward, 2018; Bowling, 2018; Ebisch et al., 2008; Hubbs, 2018; Michael Schaefer, Rotte, Heinze, & Denke, 2013a; Ward & Banissy, 2015; Ward et al., 2018); and

(6) "Another point in time": Studies that presented a prerecorded video of the illusion to the participant; therefore, stimulation does not directly cause an effect (Michael Schaefer, Xu, Flor, & Cohen, 2009; Schaefer, Konczak, Heinze, & Rotte, 2013b).

Core Concept

As described earlier, the 14 studies originally sourced, two (Acerra & Moseley, 2005; Acerra, Souvlis, & Moseley, 2005) were grouped as part of a thesis (Acerra, 2007) and with additional unpublished data from this thesis reported as A, B, C, and D for the purpose of this review. The remaining included studies are reported (Case, Gosavi, & Ramachandran, 2013; Giummarra, Georgiou-Karistianis, Nicholls, Gibson, & Bradshaw, 2010; Helmchen, Palzer, Münte, Anders, & Sprenger, 2013; Hoermann, Franz, & Regenbrecht, 2012; Hunter, Katz, & Davis, 2003; Krämer, Seddigh, Lorimer Moseley, & Birklein, 2008; Peterzell et al., 2010; Ramachandran & Rogers-Ramachandran, 1996; Ro, Wallace, Hagedorn, Farnéé, & Pienkos, 2004; Sathian, 2000; Takasugi et al., 2011; Wand et al., 2014). One of these studies was only accessible as an abstract case report (Peterzell et al., 2010). The studies (or experiments within studies) assessed a total of 486 participants, ranging from 1 to 77 participants per study. They were categorized into studies on health and disease, with the specific conditions (Table 3).

Details of the included studies are shown in Table 4.

In summary, procedures varied in terms of areas (palm vs. dorsum), stimulation time (20 s–6 min), stimulation nature (pointy or larger pressure to brushing), and tools (Semmes-Weinstein Filaments to Q-tips, spatula, brush or copper band, exposed end

Table 4. Populations, procedures, timing, and materials

Main author/ study design	Population	Procedures	Timing	Materials
Acerra, 2007 (A) Experiment with control group, no randomization, cross-sectional	10 CRPS Nine neck-related shoulder pain Nine non-CRPS localized pain, Nine healthy subjects Five CRPS reassessed	Stimulation on 30 dorsal and 34 volar points of hand and wrist with light touch, punctuate touch, and cold	One stimulation at each point	Mirror box; pen lid, exposed tip of paper clip, ice
(B) Cohort with restest	77 patients postradius fracture	As above, exposed tip of paper clip only	As above	Mirror/partition Exposed tip of paper clip
(C) Cohort	70 stroke patients within 2 weeks poststroke	As above	As above	As above
(D) RCT with control group: MT versus sham (only assessments were relevant)	40 stroke patients within 2 weeks poststroke; 40 reassessment after 2 weeks 40 reassessment 1 month postintervention	As above	As above	As above
Case et al., 2013 (Experiment 2) Three different groups, blinding of participants and assessor to group allocation	Experiment 2 only: 54 healthy psychology students	Touch of creamed face: 1) moisturizer 2) "tingly" cream (tiger balm) 3) numbing cream (lidocaine 5%)	42 trials, one per second; 42 touches on right side only, 20 bilateral; touching on face	Mirror configuration (three adjacent mirrors, like a bathroom mirror cabinet); cotton buds
Giummarra et al., 2010 Experiment with controls, no blinding, no randomization	14 upper limb amputees over 6 years postamputation 14 lower limb amputees and 12 nonamputees	RH first, then own hand, exposed to potentially threatening stimuli	13 different stimuli	Mirror box, two highly realistic rubber hands; several stimuli. Relevant only for touch: cotton bud and spatula
Helmchen et al., 2013 Experiment with control group, Exp 1: mirror scratching sitting at table Exp 2: video laying supine, real-time video display	26 male healthy volunteers	Histamine-dihydrochloride (0.03 ml, 1%) injected on palmar forearm, two trials. Condition C: scratching with six even strokes, 6 cm in length; Exp 2: as above, using real-time videoing	Six even strokes; each stroke lasting 2.5 s	Large mirror; L-shaped copper elastic band ($1 \times 10 \times 130$ mm) with rounded edges (force 100 ± 5 g)
Hoermann et al., 2012 Experiment (proof of concept study), two conditions relevant (of three), quasi-randomized for order of testing, not explained how. No blinding	21 healthy subjects	(1) Mirror box (2) Screen showing stim hand reflected	Each finger was stroked in each condition 25 times, pace of 1 Hz, order of fingers randomized (>2 min in each condition)	Short handled hog-hair flat brush size 16; mirror box and video screen
Hunter et al., 2003 Experiment, no stats With sequence of testing. Only phase 2 condition (i) was relevant. Design includes semi-structured interview and videotaping	13 upper limb amputees 1.5–14 months after amputation	Only phase 2(i) of testing for the mirror-box illusion is relevant; first with eyes closed, then open	2–5 times at each location randomly	Mirror box, cotton bud, brush

Continued

Table 4. Continued

Main author/ study design	Population	Procedures	Timing	Materials
Krämer et al., 2008	12 neuropathic pain patients (non-CRPS)	Five brush strokes with 3 s interval between	Speed: one per 2 s	Brush, 2.5 cm wide, soft; mirror
Peterzell et al., 2010 Case report Abstract only	One LL amputee	Touching of the intact leg or foot	Effect could continue for a minute lasted for up to a minute	Mirror, touch
Ramachandran and Rogers-Ramachandran, 1996 Experiment	Four UL amputees Four healthy subjects	4 of 10 patients relevant: (R.L.) (J.P.) (D.B.), and (L.C.). Various applications, for example: 16 stimuli, 8 on dorsum, 8 on palm (4 transverse, 4 coaxial)	Delay of 2–4 s. Before onset of SR and a persistence of the sensation afterwards, consistent across trials and patients. Repetitions on several occasions	R.L. Q-tip; J.P. and L.C. 15 touch stimuli and also rub and massage at home (by brother); in D.B. and J.P. also SW filaments
Ro et al., 2004 Four experiments	30 relevant healthy subjects over three experiments: Exp1:12 Exp 2: eight relevant (of 16) Exp 3: 10	Four experiments: (1) mirror brushing (2) mirror versus viewing unbrushed hand (3) mirror brushing (longer detection rating)	125 brush strokes in 2.5 min on dorsum of hand	Mirror 30.5 × 30.5 cm Exp 1: two brushes (small and large); Exp 2–4: only large brush; hand strapped onto wooden block
Sathian, 2000 Experiment	Six patients with sensory loss plus unspecified number of stroke patients with intact sensation and healthy subjects	Mirror first, then testing for inter-manual referral	3–5 trials of pressure sensations	Mirror box; bare end of cotton swab
Takasugi et al., 2011 Experiment	Part 1: 21 healthy subjects Part 2: 16 healthy subjects	In supination; stimulation with filament on fingers, palm, thenar, and forearm Exp1: own hand, then assistant's hand or vice versa; then opposite side; Exp2: own hand, rubber hand	1 Hz, 20 times, randomly	Mirror box; SW filaments 300 g
Wand et al., 2014 Randomized, repeated-measures crossover experiment with blinded assessor, each condition once	14 patients with chronic numbness posthand surgery	Condition a relevant: (a) stimulation with mirror	2 min each type of stimulation = 6 min overall; dorsum of hand; Ten Test; SW	Mirror in triangle (UL) or large mirror (LL), stroking with cotton swab, brushing with paint brush, prick with medipin

Note: CRPS = complex regional pain syndrome; SW = Semmes Weinstein Monofilaments; UL = upper limb; LL = lower limb; (R.L.), (J.P.), (D.B.), and (L.C.) are initials from patients; MT = mirror therapy; RCT = randomized controlled trial.

of pen lid, paper clip, cotton bud, or medipin). Acerra (2007) applied punctuate pressure to 30 volar and 34 dorsal points. All others applied stimulation in a less organized way or on only a few landmarks of the hand.

All studies investigated RS on hands with the effect on the contralateral hand with the exception of three: Acerra (2007), who stimulated feet in two patients with CRPS (A); Krämer et al. (2008), who stimulated areas of neuropathic pain across the body; and Case et al. (2013), who stimulated the face with the help of a double-mirror reflection. Giummarra and Takasugi (Giummarra et al., 2010; Takasugi et al., 2011) also applied stimulation to a replacement: a rubber hand (both) and another person's hand (Takasugi et al., 2011). The studies used a range of stimulation tools and strengths of stimulation, with mirror boxes, mirrors, and one artificial projection.

Outcomes

Response defined as positive by reporting RS on one occasion during the experiment in all studies reporting RS response directly. Strength of the perception was also reported in some studies. The visual analog scale was mostly used. This required using pen and paper following the experiment to give a retrospective rating of the highest RS intensity experienced. Wand et al. (2014), however, used the "Ten Test," which is a comparative rating of sensation in the affected (target) limb compared with the unaffected (stimulation) limb, using the numeric rating scale, a modified 11-point scale where the unaffected limb scores 10 for sensation on stimulation. This test requires stimulating the participant on both limbs prior and postexperiment to determine the difference in strength of the perception compared with the unaffected hand.

The intensity of the perception was reported to be 1.54 and 2.0 mean for cotton bud (rubber hand and own hand, respectively) (Giummarra et al., 2010), 1.76 (Hoermann et al., 2012), and a median between 0 and 3 (Takasugi et al., 2011). Prevalence of RS was reported in the included studies across a wide spectrum of conditions, ranging from 0% to 100% (Table 5). Some studies evaluated RS strength itself, others the enhancement of perception afterwards or the level of threshold required before RS occurred. No study reported more than 3/10 in strength as a median or mean intensity of RS with one study reporting zero strength of RS.

The identified studies reported no RS in "other pain." "Other pain" included postherpetic pain, pain from syringomyelia, radiculopathy, cervical spinal stenosis, arm plexopathy, intercostal neuropathy, infrapatellar nerve neuralgia, pelvic plexopathy, and ulnar neuralgia with five quick brush strokes (Krämer et al., 2008); shoulder pain and other neck-related pain (Acerra, 2007). Pain was mentioned as an outcome when 300 g monofilaments were used (Takasugi et al., 2011).

Table 5 shows the outcomes of all included studies grouped by population. When counting single RS tests, the scoping review includes at least 839 tests. Grouped into populations of healthy subjects and the relevant medical conditions, the number of tests range from 14 (in postnerve graft surgery) to198 (in stroke). These are shown in Table 6.

Concept of RS

There were diverging viewpoints on the nature of RS. Acerra's (2007) research group used the "synchiria test" in CRPS patients and found that symptoms could be evoked on the affected limb when stimulating the nonaffected limb with a pointed tool and watching this in the mirror at midline. With this test she was able to map out allodynia and paresthesia precisely on the contralateral, affected limb in 10 patients with CRPS, and to predict all 25 of the 77 postradius fracture patients who would develop CRPS later, though with some false-positive results. In the subsequent studies of her thesis, she documented a positive "synchiria test" in 38 out of 70 patients early after stroke and found reduced rates in a sample of 40 early stroke patients after 2 weeks of (movement based) MT or control. This study showed 17 responders at baseline, 10 after 2 weeks, and 11 after 6 weeks. There was no significant difference between intervention and control group, indicating that RS resolved over time in the early phase after stroke. All of Acerra's experiments portrayed RS as a sign of pathology. Prodding with a pointed tool was used as a test that provoked pathological symptoms. It was not used in a way that may improve sensory perception.

Wand and colleagues (2014), on the other hand, used RS stimulation to improve sensation after peripheral nerve damage post hand-surgery. They used RS as a rehabilitation tool, eliciting improvements after only one application. Helmchen and colleagues (2013) described itch relief through mirror scratching, using RS to alleviate symptoms.

Discussion

The format of a scoping review met the objectives of this study, namely to map out existing evidence of RS (referral of sensation) with boundaries of the concept RS, keywords, prevalence, procedures, and tools, and with these answered the research question of what is known about the effect of RS. The findings highlight several issues, which will now be discussed in more detail.

Table 5. SR occurrence grouped by condition

Population	Study	Number of relevant subjects	Relevant test conditions	Outcome (SR unless specified)
Healthy subjects (no altered conditions)	Acerra, 2007	9	Own hand	0
	Hoermann et al., 2012	21	Own hand/projection	9 (42.9%)
	Takasugi et al., 2011	Exp.1: 21 Exp.2: 16	Own hand	5 (38%) 10 (62%)
	Ro et al., 2004	Exp.1: 12 Exp.2: 8 (of 16) Exp.3: 10	Own hand	"many subjects reported . . . feeling something"
	Giummarra et al., 2010	12	Rubber hand/own hand	Cotton bud: 4 (15.4%) Spatula: (23.1%)
	Ramachandran and Rogers-Ramachandran, 1996	4	Own hand	0
	Sathian, 2000	(no number)	Presumably own hand	0
Healthy subjects (altered conditions)	Case et al., 2013	54 (18 per group)	Three groups: tingly cream, moisturizer, and numbing cream	Touch confusion: 25%, 30%, and 50%, respectively
	Helmchen et al., 2013	26 male	Histamine injection, mirror scratching	30%–50% itch relief under this condition
	Giummarra et al., 2010	12	Rubber hand	Cotton bud in a mixed sample: 12 (46.2%) Spatula in a mixed sample: 13 (50%)
	Takasugi 2011 Experiment 1 Experiment 2	21 16	Other person's hand Rubber hand	21 (85.7%) 21 (100%)
Stroke	Sathian, 2000	A: six (five stroke and one post brain surgery) B: two stable sensory loss C: hemiparetic patients without sensory loss (no number)		A: 6 (100%) B: 0 C: 0
	Acerra, 2007	Acute stroke patients (within 14 days post stroke) A: ($n = 70$); B: ($n = 40$)	Own hand	A: 38 (54%) B: baseline: 17 (43%), after 2 weeks: 10 (25%); 1 month postintervention: 11 (28%)
PLP	Giummarra et al., 2010	14 LL amputees	Own hand Rubber hand	Cotton bud: 4 (28.6%) Spatula: 3 (21.4%) Cotton bud: 6 (42.9%) Spatula: 7 (50%)
	Peterzell et al., 2010	One LL amputee	Own foot	1
	Hunter et al., 2003	13 amputees	Phase 2 (i)	No new or additional effects to effect without mirror (7)
	Ramachandran and Rogers-Ramachandran, 1996	Four (R.L., D.B., J.P., and L.C.)		4 (100%)

Continued

Table 5. Continued

Population	Study	Number of relevant subjects	Relevant test conditions	Outcome (SR unless specified)
CRPS	Acerra, 2007	10	Eight own hand Two own feet	10 (100%) dysynchiria
Postradius fracture	Acerra, 2007	77 baseline 77 assessment 2	Own hand	27 (35%) 23 (29.9%)
Other pain	Acerra, 2007	Nine shoulder pain and nine other postsurgery pain	Own hand	0
	Krämer et al., 2008	12 neuropathic pain patients	Eight hands, one forearm, two thorax, one thigh, one knee	0
Postnerve graft surgery	Wand et al., 2014	14 patients	One session of own hand	N/A.; (24% increase of sensory abilities)

Note: PLP = phantom limb pain; CRPS = complex regional pain syndrome; LL = lower limb; (R.L.), (J.P.), (D.B.), and (L.C.) are initials from patients.

Table 6. Count of tests (including reassessments of the same participants) and summarized responder rates

Population	Number of participants	SR response
Healthy subjects	>113[a]	0%–62%
Healthy subjects altered conditions	129	25%–100%
Stroke patients	198	0%–100%
CRPS patients	169	100%
PLP patients	32	0%–100%
Postradius-fracture patients	154	29.9%–35%
Other pain conditions	30	0
Postnerve graft surgery	14	24% increase of sensory abilities
Sum	>839	0%–100%

Note: PLP = phantom limb pain; CRPS = complex regional pain syndrome.
[a]*n* was unclear in Giummarra and colleagues (2010).

First, the identified body of literature was mostly situated within an experimental context, with cross-sectional studies except one study evaluating RS response before and after MT (Acerra, 2007), and another as a one-off treatment itself (Wand et al., 2014). This demonstrates a lack of research into usefulness of RS in rehabilitation.

Second, stimulation tools and procedures differed between studies. Pointy stimuli were reported to cause pain in two studies (Acerra, 2007; Takasugi et al., 2011). If cotton buds and brushes also achieve RS, such gentle tools may be preferable to 300 g monofilament or the end of a paper clip in a rehabilitation context. Whether stimulation with gentle tools achieves RS without pain reaction can be assessed with an experiment using healthy participants.

Third, the populations included participants in health as well as in disease. The studies claiming no RS response in healthy subjects or pain other than PLP or CRPS (Acerra, 2007; Krämer et al., 2008; Ramachandran & Rogers-Ramachandran, 1996; Sathian, 2000) reported on low numbers of up to 12 subjects. The larger studies, however, focusing on overall 229 healthy participants (Case et al., 2013; Giummarra, Bradshaw, Nicholls, Hilti, & Brugger, 2011; Helmchen et al., 2013; Hoermann et al., 2012; Ro et al., 2004; Takasugi et al., 2011), reported between 9% and 100% RS response. This gives reason to believe that the healthy human brain is susceptible to touch perception mediated through a visual illusion and challenges the view that RS response indicates malfunctioning neural processing. As such, RS may be useful as an intervention rather than as a test of pathology, which suggests assessment of the effect in a population of stroke patients with numbness.

Fourth, there was no description of how the effect develops over time if stimulation continues. The procedure of tailoring an intervention to elicit the desired outcome is usual in rehabilitation. Therefore, it is necessary to investigate the effect itself, how RS perception develops over time, whether there are unwanted effects on longer stimulation, and to which end sensory abilities can be restored, or disturbed, in disease. If sensory abilities can be improved in stroke patients suffering from numbness and at risk of cuts, burns, and bruises as a result, then such damage could be avoided. In addition, sensory loss is well known to impair motor abilities (Dimitrijevic, Stokic, Wawro, & Wun, 1996; Sullivan & Hedman, 2008; Taub & Uswatte, 2003). Therefore, improved sensory perception is likely to facilitate motor rehabilitation outcomes. If sensory abilities can be unlocked or enhanced with a simple and easy procedure such as RS stimulation, when carefully applied to avoid pain, it may be highly valuable for patients suffering from sensory impairment. A study with healthy participants using stimulation over time and exploring any changes or development of RS will be able to assess this effect.

A further question arises from these points: "what, if not disease, makes an RS-responder"?

Perhaps, normal neuropsychological processes play a role such as individual differences. For example, variations in personality disposition may be important with levels of individual agreeableness, conscientiousness, or openness to experience. Particular strengths or weaknesses in such traits may facilitate transition from visual to haptic perception. Cognitive style may also influence responses. In an earlier study, expert practitioners were divided on the question, whether "very analytical . . . patients have difficulties with MT" (Hagenberg & Carpenter, 2014), indicating that frames may be more important to nonresponders than content, perhaps spoiling the illusion. Therefore, the way that individuals consider and process information (Baron-Cohen, Richler, Bisarya, Gurunathan, & Wheelwright, 2003) relating to RS could be important. Furthermore, individual differences around susceptibility and suggestibility may be considered. The RHI embodiment correlates with susceptibility and suggestibility (Haans, Kaiser, Bouwhuis, & Ijsselsteijn, 2012; Marotta, Tinazzi, Cavedini, Zampini, & Fiorio, 2016). However, suggestibility does not influence the ability to locate touch (a top-down process in the RHI) (Marotta et al., 2016). As RS response was particularly high when a rubber replacement was stimulated, suggestibility is unlikely to be highly relevant. Higher level of education has been reported to increase benefit from MT home-based exercising program (Darnall & Li, 2012). All such factors could be assessed in a future study on RS. However, several studies with large sample sizes would be required before patient selection should be based on individual differences.

One strength of this study was the design as a scoping review, allowing mapping out different experimental contexts from a variety of disciplines and enhancing understanding of concepts. These perspectives and factors are essential for future study design to understand normal neural processing across disciplines. In addition, the development of a map enables future studies to be instantly allocated to the relevant body of literature, which facilitates the design of future systematic reviewing. However, unpublished experiential knowledge among practitioners may also be present, as MT practice protocols mention external stimulation, indicating usefulness of future qualitative research exploring tacit knowledge from practitioners. Nonetheless, the mapping and identified concepts render future studies easier.

Conclusion and Implications

In summary, the results from this scoping review suggest that RS can be elicited in healthy participants in a mirror setting. Highly interesting is the finding that our understanding of normal cognitive and neurological processing can be challenged, as a simple visual illusion can create touch perception even in healthy people. If sensory pathways are malleable enough to be changed by RS stimulation, adapted application may be able to improve sensory impairment. Before further studies can be undertaken, a protocol needs to be developed and tested in a wide range of healthy people. This protocol should incorporate the evaluation of all of the following: (1) responder characteristics; (2) real or potential risks; (3) longer term effects; (4) optimal selection of stimulation type and intensity; and (5) optimal choice of tools, general equipment, and overall procedures.

The increasing amount of reputable research interest in the phenomenon of evoked RS, the indications of potential benefit in rehabilitation mentioned by most authors, and the lack of research into such support the need for further study of RS development. On the whole, the role of vision in rehabilitation of sensory perception may very well have been underestimated to date.

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Conflict of Interest

AH occasionally teaches courses in mirror therapy. DGL, SJ and JM have no conflict of interest. TGR is a National Institute for Health Research Senior Investigator. The views expressed by the author(s) are not necessarily those of NIHR or the Department of Health and Social Care.

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