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Enhanced early sensory outcome after nerve repair as a result of immediate post-operative re-learning: A randomized controlled trial

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Abstract

We assessed the use of guided plasticity training to improve the outcome in the first 6 months after nerve repair. In a multicentre randomized controlled trial, 37 adults with median or ulnar nerve repair at the distal forearm were randomized to intervention, starting the first week after surgery with sensory and motor re-learning using mirror visual feedback and observation of touch, or to a control group with re-learning starting when reinnervation could be detected. The primary outcome at 3 and 6 months post-operatively was discriminative touch (shape texture identification test, part of the Rosen score). At 6 months, discriminative touch was significantly better in the early intervention group. Improvement of discriminative touch between 3 and 6 months was also significantly greater in that group. There were no significant differences in motor function, pain or in the total score. We conclude that early re-learning using guided plasticity may have a potential to improve the outcomes after nerve repair.

Level of evidence: II

Keywords

Nerve repair, re-learning, targeted plasticity, mirror visual feedback, rehabilitation

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Introduction

Changes occur in the brain within minutes after a peripheral nerve transection, when the peripheral receptors and muscles are disconnected from the cerebral sensorimotor systems. These changes, which are influenced by several biological and psychological factors, are part of a dynamic process in the brain that continues during the nerve regeneration and reinnervation period (Chen et al., 2002; Kandel et al., 2013). Extensive changes in the primary somatosensory cortex (S1) and the motor networks in the brain result from substantial misdirection of the regenerating nerve fibres, which reinnervate incorrect peripheral targets, i.e. muscles and peripheral receptors. The normal somatotopy order in the S1, where distinct groups of neurons process sensory information from specific fingers, is broken down to a more disorganized pattern (Allodi et al., 2012; Chen et al., 2002; Kandel et al., 2013; Pourrier et al., 2010; Wall et al., 2002). There are numerous factors that influence the functional outcome, such as the age of the patient, type of injury, timing of surgery and cognitive capacity (Kandel et al., 2013; Lundborg, 2004; Rosén et al., 1994). In addition, motivation and adherence to the rehabilitation regime are also important factors (Jaquet et al., 2002).

The time when sensory and motor re-education is started may also be important. Sensory re-education

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programmes have traditionally been used to enhance function after nerve repair (Miller et al., 2012; Rosén and Lundborg, 2011); however, they are commonly started once touch can be perceived in the hand (Dellon, 1981; Wynn-Parry and Salter, 1976). This is usually several months after the injury, by which time, profound cerebral reorganization may already be established.

The re-learning process after a nerve injury has been divided into two overlapping phases (Lundborg and Rosén, 2007). In Phase 1, the injured nerve does not transmit any signals, the skin area innervated by the injured nerve is without sensibility and the muscles do not function. This phase lasts up to 3 months after an injury at wrist level, by which time some re-growing axons have reached the end organs. Although traditionally no active re-education is carried out in this period, it has been suggested that re-learning in Phase 1 should be aimed at activating and maintaining the neurons in the brain that originally connected with the injured nerve, in order to prepare these neurons for the time when the nerve has regenerated and starts to send signals (Lundborg and Rosén, 2007). Phase 2 starts when the outgrowing axons have reinnervated the skin at fingertip level and muscle activity can be identified. At this time, rehabilitation can be aimed at re-establishing and strengthening the neural connections in the somatosensory and motor systems in the brain that process information to and from the previously injured nerve.

New knowledge about the capacity of the brain to change and adapt (brain plasticity) has improved our understanding of cerebral changes after a peripheral nerve injury. Furthermore, it has also opened the possibility of using guided plasticity to substitute or improve functions that have been damaged or lost due to injury (Duffau, 2006). The cross-modal capacity of the brain (the interaction between different senses) (Pascual-Leone and Hamilton, 2001) can, for example, be used to create an illusion of activity from the injured area, which may enhance the relearning process. Mirror visual feedback (MVF) is a potential training technique for this purpose (Ramachandran et al., 1995; Rosén and Lundborg, 2005). Visual observation of activity has been demonstrated to activate motor (Rizzolatti, 2005) and sensory areas in the brain (Avikainen et al., 2003; Grezes et al., 2003; Hansson et al., 2009; Keysers et al., 2004), and has been shown to improve motor learning after stroke and to influence sensibility in the hand (Michielsen et al., 2011; Ro et al., 2004). Thus, MVF may be a way to stimulate the S1 and motor network in Phase 1 and hence prepare those cerebral areas deprived of their normal input through the injured nerve, for when the nerve has regenerated (Phase 2).

Our hypothesis was that guided plasticity training using MVF with movements of the hand and observation of touch, directly after repair of transected median or ulnar nerves, combined with traditional training in Phase 2 rehabilitation, when the outgrowing axons have reinnervated the skin and muscles, would result in better sensory and motor function than traditional re-learning alone.

Methods

Trial design

The study design was a prospective randomized multicentre study involving three hand centres: the Department of Hand Surgery Malmö, Lund University, Sweden; the University Hospital of South Manchester, the University of Manchester, UK; and the Department of Plastic & Reconstructive Surgery and Department of Rehabilitation Medicine, Erasmus MC Rotterdam, The Netherlands. The study was approved by the Ethical Committee at Lund University, the UK National Health Service National Patient Safety Agency and at the Erasmus MC. The study was conducted according to the declaration of Helsinki. All participants gave written consent.

Patients were randomized to either the Phase 1 intervention group, with sensory and motor re-learning starting within the first post-operative week, according to a standardized protocol with the use of MVF and observation of touch exercises during the first 6 post-operative months, or to the control group, with sensory and motor relearning starting when some reinnervation in the hand could be documented.

Randomization

Block randomization with a block size of eight per centre was used. We used numbered sealed opaque envelopes for each centre and the patients were randomized within 1 week after surgery by opening consecutive envelopes. The envelopes were made by a researcher not involved in the inclusion of the patients, and neither the researchers nor the patients were aware of the block size.

Sample size

The primary outcome measure for the investigation was discriminative touch (shape texture identification (STI) test; part of the Rosen score; see below under 'Outcomes' for explanation.). The sample size estimation was based on results on the STI test with a standard deviation (SD) of 1.04 (Rosén, 2003). To detect a statistically true difference of 1.2 units on the

STI test, with a power of 80% and p-value ≤ 0.05, 12 patients in each group were required for a two-sided analysis.

Participants

A total of 37 consecutive patients with a median or ulnar nerve injury at wrist or distal forearm level were included between 2006 and 2011. Inclusion criteria were: adult (18–70 years) patients with acute complete median or ulnar nerve transections at the wrist or distal forearm level (maximum 10 cm proximal to the wrist) and primary nerve repair within 1 week. Nerve injuries combined with injuries to tendons and vessels was also included.

Exclusion criteria were: reconstructive surgical procedures, including nerve tubes or grafts; severe psychiatric disorders or drug problems; self-inflicted injury; nerve injuries at more than one level; combined median and ulnar nerve injuries; fractures or amputations; and communication problems due to language difficulties.

Study intervention

General post-operative regime. Both groups received the same general post-operative regime and had an equal number of treatment and follow-up sessions. During the immobilization period, a standard post-operative regime was followed to protect the repair site. Wound care, active range of motion exercises, grasping, fine manipulative exercises and prevention of contracture from paralysed muscles by splinting were started after the immobilization period or when appropriate for the injury. Patients were educated about how to protect the insensate hand, and advised how to integrate the re-education in activities of daily living. Limitations in carrying out activities of daily living were addressed by teaching coping strategies and the provision of assistive devices. After nerve repair at the wrist level, gentle exercises to regain mobility of the wrist were normally started 3–4 weeks after surgery. Exercises were gradually increased and strengthening exercises were introduced when appropriate. Light activities were resumed at 6 weeks after nerve repair but with due consideration of the imbalance from the paralysed muscles. Full loading was normally allowed after 12 weeks. All patients were given information about hyperaesthesia and cold sensitivity. Desensitization exercises and advice about how to deal with cold sensitivity were provided when necessary.

First week after surgery to 12 weeks after surgery. Phase 1 training with MVF and observation of touch: patients were provided with oral and written instructions on the exercises to be done at home 4–5 times a day in brief periods (maximum 10 min). The patients borrowed a standard mirror and MVF-instructions were:

> Simply look at the reflection without moving either of your hands. Concentrate hard on the mirror reflection for about one minute. You can name your fingers and part of your hand while you watch the mirror image. Once you are comfortable with this, slowly start to move your unaffected hand while you watch the mirror image. You should do this for a few minutes. Now move both hands in exactly the same way while looking at the reflection in the mirror (specific exercises depending on which nerve is injured).

Observation of touch was implemented by synchronous touch of both hands, including the areas without sensibility. Instructions to the patient were:

> You can ask someone to touch the insensible fingers and at the same time touch the corresponding finger on the other hand. You watch and concentrate on the touch. Alternatively you can yourself touch your finger with the corresponding finger of your opposite healthy, hand".

Both MVF-training and the observation of touch were carried out mainly on a home training basis according to the description above. However, the patient was also seen by the therapist regularly during the first 6 weeks and then monthly until the end-point of Phase 1 was reached.

Control group: the general post-operative regime was applied but without the Phase 1 training described above, and the same number of follow-up sessions were undertaken during the first 12 weeks as in the Phase 1 intervention group.

Twelve weeks after surgery. Both groups received a standard information folder based on classic sensory re-education principles (Dellon, 1981; Wynn-Parry and Salter, 1976). A home programme was introduced based on training several times per day (five times a day was suggested) when some perception of touch/pressure (Semmes–Weinstein monofilament, SWM) could be detected in the palm of the hand. Initially, localization exercises were done. Discriminative exercises with identification of different objects, textures and shapes were started when some protective sensibility (SWM #4.31/#4.56) could be detected at fingertip level, which normally occurs 5–6 months after repair at wrist level (Rosén and Lundborg, 2011).

Outcomes

Therapists experienced in assessment after nerve repair carried out the assessments at 3 and 6 months after surgery. The therapists were not blinded for the treatments that had been given.

Primary outcome. The primary outcome was discriminative touch. Discriminative touch is one part of the sensory domain of the Rosen score that was used as the test instrument. The Rosen score is a composite diagnosis-specific clinical evaluation instrument used after nerve repair and consists of three domains: sensory, motor and pain/discomfort (Rosén and Lundborg, 2000). Each domain comprises specific assessments and each assessment, as well as each domain, produces a mean score of between 0–1. The score of each instrument is quantified between 0 and 1, and is the quotient between the result obtained in each test and the 'normal' result. For example, a two-point discrimination (2PD) of 10 mm gives a score of 2/3 = 0.67, and 2 of the maximum 6 points in the STI test gives a score of 0.33 (Rosén and Lundborg, 2000). The total score is the sum of the three domains and the maximum score is 3, which indicates normal sensory and motor function without pain.

- Sensory domain: Cutaneous touch/pressure thresholds were measured at three critical sites for the median and ulnar nerve, respectively, using SWMs (ASHT, 1992). Tactile gnosis was measured using static 2PD (ASHT, 1992) and the STI test (Jerosch-Herold, 2005). Dexterity was measured using tasks 4, 8 and 10 of the Sollerman hand function test (ASHT, 1992)
- Motor domain: Assessment of muscle contraction force was performed using manual muscle testing (Brandsma et al., 1995). Grip strength was measured with the Jamar dynamometer (Mathiowetz et al., 1984).
- Pain/discomfort domain: A four-graded scale was used for the patients' estimation of problems from hyperaesthesia in the autonomous zone of the nerve and cold intolerance, respectively (Rosén and Lundborg, 2000).

Analyses

All analyses of data were carried out on an intention-to-treat basis. Results for each group are presented with means and SD. *T*-tests were used and differences between groups are presented with means and 95% confidence interval (CI). The level for significance was 0.05.

Results

Recruitment

A total of 37 patients were enrolled and randomized. Recruitment started in 2006 and ceased in 2011 because inclusion was too slow. There was an imbalance in recruitment and follow-up between the three centres (Figure 1). Figure 1 illustrates the numbers of participants in the study over time. Owing to drop-outs and missing data, 29 patients were assessed with the primary outcome instrument according to the protocol at 3 months, and 27 at 6 months follow-up. The minimum number of patients in each group for the calculated power of 80% with two-sided analysis, were available at 3 and 6 months, but numbers were inadequate for follow-up after 6 months. The demographics of the two groups at 3 months follow-up are shown in Table 1. The demographic profile of the drop-outs between randomization and first follow-up did not differ from that shown in Table 1.

Outcome

The results are shown in Table 2 and Figure 2. Follow-up at 3 and 6 months in the patients with Phase 1 intervention showed significantly better discriminative touch at 6 months. The improvement of discriminative touch, between 3 and 6 months, in terms of STI test results, and two-point discrimination, was also significantly greater in the Phase 1 intervention group. The raw data for the STI test assessments are shown in Table 2. The mean values and 95% CI of the results in each study group for specific functions contributing to the sensory domain of the Rosen score-up are illustrated in Figure 2. Ongoing improvement was seen in all the parameters in the Rosen score in both groups over the 6 months period, with a total score of 1.5 (SD 0.4) in the intervention group and 1.3 (SD 0.25) in the control group, both within the normal range (Galanakos et al., 2011; Lundborg et al., 2004; Vordemvenne et al., 2007). No significant differences in motor function, pain/discomfort or in total score were seen between the intervention and control groups.

Discussion

The misdirection of the outgrowing axons and the cortical reorganization process that occur after a nerve injury produce new signal patterns from the peripheral receptors to the brain and from the brain out to the muscles, and these new signal patterns have to be learned. Learning is likely to be easier if the somatosensory area and the motor network have been stimulated during the early phase after a nerve injury, thus preparing these areas for when the axons have re-grown. This cerebral preparation can be achieved by techniques such as MVF.

Our hypothesis was that guided plasticity training using MVF from the injured hand and observation of

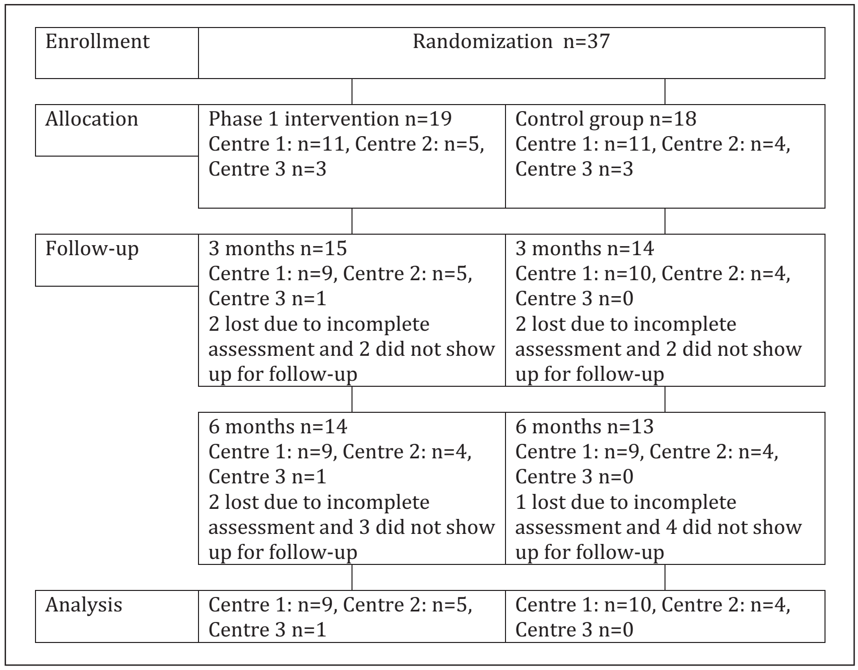

Figure 1. Flow chart of participants.

Table 1. Demographic data of the 29 patients at the 3 month follow-up.

	Phase 1 intervention group *n* = 15	Control group *n* = 14
Gender (male:female)	6:9	14:0
Dominant hand injured	10	6
Age at injury (median, range)	40 (19–63)	41 (18–69)
Smoker	4	4
Injured nerve (median:ulnar)	3:12	6:8
Tendon injury	14	13
Cause of injury		
Glass	11	7
Knife	3	3
Machine	0	3
Other	1	1
Suture material		
8–0	7	10
9–0	7	4
10–0	1	0
Epineural repair	15	14

touch, immediately after repair of transected median or ulnar nerves, combined with traditional rehabilitation, would result in better sensory and motor function during the first 6 months after surgery than traditional delayed re-learning alone.

Our results partly support that hypothesis. Phase 1 intervention, with sensory and motor re-learning starting in the first week after surgery, was beneficial for early recovery of discriminative touch (Table 2).

A few studies that have successfully used early sensory re-learning have been published. Cheng and colleagues reported outcomes after digital nerve repair (Cheng, 2000; Cheng et al., 2001). In another study, with similar injuries to those in the present study, sense-substitution in the early phase after median or ulnar nerve repair was used (Rosén and Lundborg, 2007). MVF is frequently used today in hand rehabilitation (Rosén and Lundborg, 2005; Rothgangel et al., 2011; Selles et al., 2008). This is the first randomized controlled study of MVF after repair of major nerve trunks. The MVF training in this study focused on motor exercises using the illusion of function from the feedback in the mirror. The mere observation of a moving hand activates 'mirror neurons' in the premotor areas. These neurons are an important part of the motor network and this area is also believed to play a fundamental role in learning new motor skills (Rizzolatti, 2005). Stimulation of the motor network by MVF is likely to stimulate cerebral areas important for somatosensory processing, because of the finely tuned interaction between the visual and somatosensory system and the motor network (Hansson et al., 2009; Rosénkranz and Rothwell, 2012). The instruction to the patients in this study at observation of touch was:

> You can ask someone to touch the fingers that do not have sensibility at the same time as touching the corresponding finger on the other hand. You watch and concentrate. You can also touch your finger with the corresponding finger of your opposite hand.

Table 2. Discriminative touch (the primary outcome) at 3 and 6 months.

	3 months			6 months			Change 3–6 months
	Phase 1 intervention group $n = 15$	Control group $n = 14$	Difference between groups (95% CI) p-value	Phase 1 intervention group $n = 14$	Control group $n = 13$	Difference between groups (95% CI) p-value	Difference between the groups (95% CI) p-value
	Mean score (SD)	Mean score (SD)		Mean score (SD)	Mean score (SD)		
STI test 0–1*	0.05 (0.12)	0	0.06 (−0.01 to 0.12) $p = 0.33$	0.19 (0.23)	0.03 (0.07)	0.16 (0.01 to 0.31) $p = 0.02$	0.13 (0.02 to 0.22) $p = 0.018$
2PD 0–1*	0.04 (0.17)	0	0.04 (0.05 to 0.14) $p = 0.10$	0.20 (0.26)	0	0.20 (0.05 to 0.36) $p = 0.01$	0.15 (0.02 to 0.29) $p = 0.027$
	Median score (range)	Median score (range)		Median score (range)	Median score (range)		
Raw data STI test**	0 (0–2)	0 (0–0)		1 (0–5)	0 (0–1)		

2PD: two-point discrimination; STI: shape texture identification.
*Score between 0–1 (1 = normal function) (see text for details).
**Maximum score 6.

This training is a combination of sensory and motor activities by the patient, and it is likely that several cortical areas are activated. It takes concentration, an ability to visualize, and an understanding and motivation for abstract thinking to undertake this kind of training, and the difficulty in carrying out such training in a home programme is a potential bias for the study.

The recovery of discriminative touch/tactile gnosis that was shown in this study was, as usual, less than recovery of touch thresholds (Figure 2) (Chemnitz et al., 2013; Galanakos et al., 2011; Jaquet et al., 2001; Lundborg et al., 2004; Rosén et al., 2014; Vordemvenne et al., 2007). This difference can be explained neurobiologically by the facts that touch perception requires only the detection of a peripheral stimulus, whereas discriminative sensibility requires both detection and an interpretation of the stimulus. This more complex task is more difficult owing to the re-organization in the somatosensory system after nerve injury.

Re-learning can be influenced by a number of factors, such as functional use of the hand, learned non-use (Taub et al., 2006) and environmental factors, as well as specific cognitive capacities of the individual patients (Rosén et al., 1994). The fact that fewer dominant hands were included in the control group may be a source of bias in this study.

There were no significant differences in the motor functions assessed in this study between the two groups. It is possible that a more sensitive tool for measurement of intrinsic muscle function might have demonstrated such differences (Schreuders et al., 2004; Selles et al., 2006).

Limitations of the study included lack of blinding of the therapists who did the assessments, and a relatively high number of drop-outs (10 of 37). There were also fewer dominant injured hands in the control group. Recruitment was uneven between centres, with 82% of the patients coming from two of the three centres. However, because of the blocked randomization, the distribution of the patients within each centre was still balanced. The relatively high number of drop-outs and the slow inclusion rate resulted in fairly small groups, but they were still adequate for the 80% power to avoid a type II error.

In most cases the same therapist in each centre did all the assessments, so consistency in the 2PD testing in accordance with the 'Moberg-method' (ASHT, 1992) could be expected.

A recent systematic review focusing on sensory re-education programmes (Miller et al., 2012) have highlighted both the possible use of early re-learning after median and ulnar nerve repairs, and also the very limited number of studies in the field that meet with the methodological criteria for evidence-based research. Our results have clear implications for clinical work, and we conclude that our results support the use of guided plasticity mechanisms in early re-learning after nerve repair.

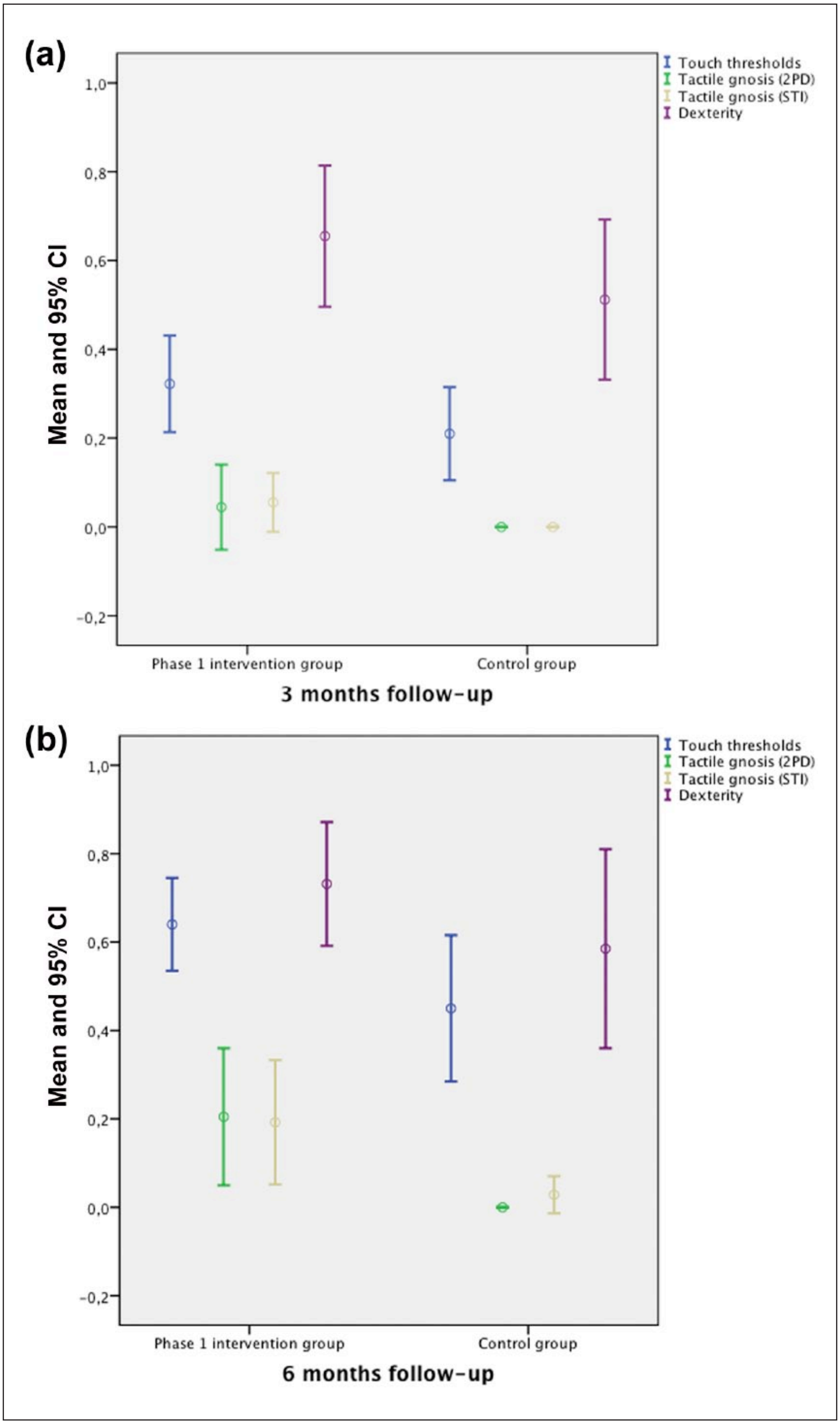

Figure 2. Error bars illustrating mean and 95% CI of results for specific functions contributing to the sensory domain of the Rosén score for each study group at (a) 3 months and (b) 6 months follow-up.
2PD: two-point discrimination; STI: shape texture identification.

Conflict of interests

None declared.

Ethical approval

Approval of the study protocol was obtained from each local Ethics Committee.

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