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Walking track analysis: an assessment method for functional recovery after sciatic nerve injury in the rat

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Walking track analysis was first described by de Medinaceli et al. This technique has been significantly modified to provide methods of indexing nerve function that are more valid. Moreover, it has been questioned by several authors. The aim of the present review is to offer a combined knowledge about walking track analysis for scientists who deal with neuroscience. (Folia Morphol 2009; 68, 1: 1–7)

Key words: walking track analysis, sciatic function index, print length, toe spread, intermediate toe spread

THE RAT SCIATIC NERVE AS A MODEL FOR PERIPHERAL NERVE REGENERATION

In the biological sciences, a number of animal models have been developed in order to study peripheral nerve regeneration. However, rats are used extensively in the biological sciences because of their small size and the availability of a large number of animals of identical genetic stock at a reasonable cost. An additional advantage is that it is easy to work with and well studied by many scientists. The sciatic nerve shows an equivalent capacity for regeneration in rats and subhuman primates [29]. For this reason, the rat sciatic nerve model is a widely used model for the evaluation of motor and sensory nerve function at the same time [11, 29].

APPROPRIATE PARAMETERS FOR THE ASSESSMENT OF PERIPHERAL NERVE REGENERATION

Nerve regeneration has been experimentally quantified using three commonly employed classes of measures: electrophysiology, histomorphometry, and functional tests such as walking track analysis [11, 30], external postural thrust [16], and ankle stance angle [26]. Selection of the appropriate assessment parameter to measure neural regeneration will be critical for the success of any experimental study. It has been assumed that these three classes are highly correlated to each other. Many nerve studies report the usage of more than one outcome measure, yet fail to report any correlation analysis. Traditional methods of assessing nerve recovery, such as electrophysiology and histomorphometry, do not necessarily correlate with a return of motor and sensory functions [11]. There is no indication of whether poor electrical results equate with poor histological results or poor function [30]. With axon count and degree of myelination studies it is not possible to know if the axon reaches the appropriate target organ or not [23, 28]. Therefore, extrapolation of the electrophysiological and histomorphometric parameters may lead to inappropriate interpretation of return of function [23, 30].

Research questions should be tested using the most appropriate measures. If the nature of the question is about functional outcome, then a functional analysis is best. However, if the research

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question relates to enhancement of fibre regeneration, then an electrophysiological or morphological analysis is more appropriate. The clinical reports, as well as the experimental results demonstrating no correlation between measures, underscore the need to consider which aspects of nerve regeneration are of interest when designing studies [23, 28].

Walking track analysis is a measure of overall coordinated distal motor function requiring intact motor and sensory functions. After nerve injury, the nerve fibres innervate the muscles aselectively; because of this, the activation patterns of the muscles is abnormal during locomotion [14]. Because maximal effort is not necessary for walking, there is no correlation between walking track parameters and maximal muscle forces [35]. Although a muscle or sensory receptor may be reinnervated, cortical control may not permit adequate muscle activation [11].

WALKING TRACK ANALYSIS

Walking track analysis was first described by de Medinaceli et al. [10] in 1982. The approach they described is utilized increasingly by the researchers who deal with neuroscience. It combines gait analysis and the temporal and spatial relationship of one footprint to another during walking (Fig. 1). Their data analysis employed a complicated mathematical formula, empirically derived, comparing four measurements between the experimental and the normal sides. The numerical value of the formula is termed the sciatic function index (SFI). This index of measuring functional recovery has been used by numerous investigators with consistent results.

DATA OBTAINED FROM WALKING TRACKS

Several measurements are taken from footprints, these are as follows:

— print length (PL): distance from the heel to the third toe;
— toe spread (TS): distance from the first to the fifth toe;
— intermediate toe spread (ITS): distance from the second to the fourth toe (Fig. 1).

All three measurements are taken from the experimental (injured) and normal (uninjured or opposite) sides [1]. Dellon and Dellon [12] discussed the validity of the normal hind limb, since it is theoretically possible that a given strain of rat will have a change in the measurements of the contralateral hind footprint parameters as a result of carrying increased weight after nerve injury to the opposite leg, it may be invalid to assume that the contralateral leg has a normal footprint. However, many authors have used the opposite leg as normal.

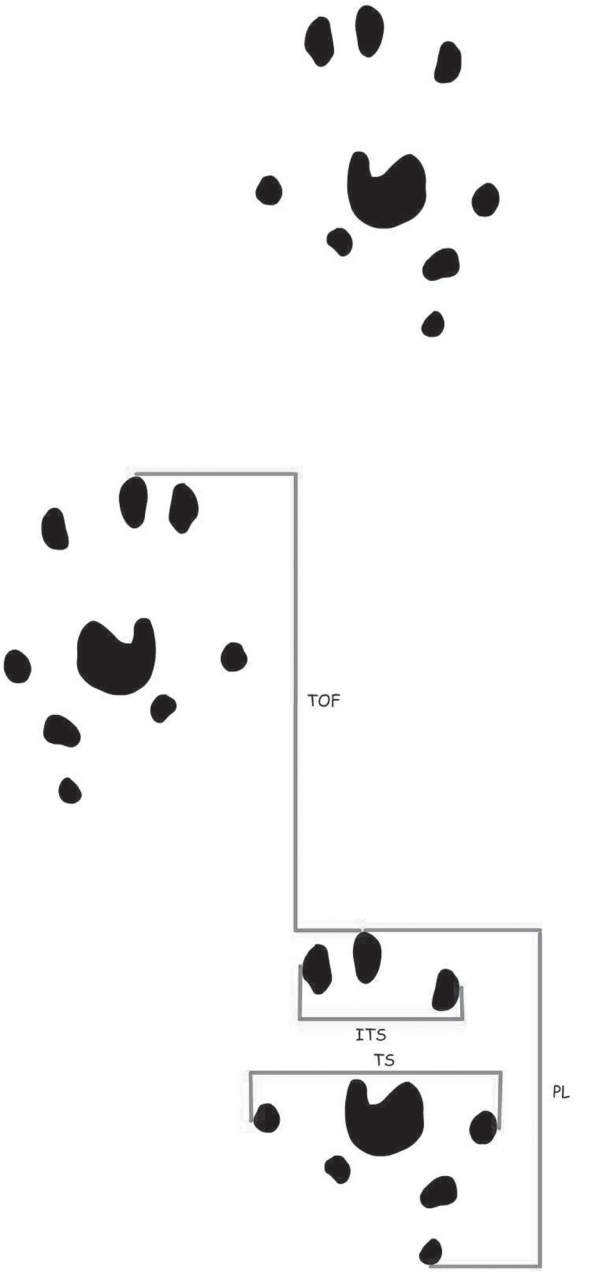

Figure 1. The temporal and spatial relationship of one footprint to another during walking; measurements are taken from the footprints; PL — distance from the heel to the third toe, the print length; TS — distance from the first to the fifth toe, the toe spread; ITS — distance from the second to the fourth toe, the intermediate toe spread; TOF — distance to opposite foot.

After obtaining the data from the tracks, they are used to calculate the index SFI. An SFI of 0 indicates

normal, and –100 indicates total impairment. However, de Medinaceli et al. [10] reported the normal values between +11 and –11. As a result, many modified calculations accept 0 as normal and –100 as total impairment [5, 9].

CHANGES AFTER SPECIFIC NERVE INJURIES

As a result of a complete peroneal nerve lesion, the toe extensors and foot dorsiflexors and evertors are denervated. Therefore, owing to the opposed action of the toe and foot flexors, the animal has a shortened print length. The distance between the intermediate toes is relatively unaffected owing to the normal functioning of the foot intrinsics. Only a slightly decreased toe spread is noted [1].

A complete posterior tibial nerve lesion results in a more significantly impaired gait and walking track. Secondary to the loss of ankle plantar flexion, foot inverters, toe flexors, and foot intrinsics, the footprint characteristically demonstrates an increased print length, a decreased toe spread and a decreased intermediate toe spread. There is also a tendency toward foot eversion. Significantly, the loss of intrinsic muscle function results in a decreased toe spread. The unopposed dorsiflexion from intact peroneal nerve function pushes the heel down, causing the animal to walk on the entire sole of the foot. This results in a longer print length [1].

A complete sciatic nerve lesion is similar to that of the posterior tibial nerve lesion; however, the pattern attributable to the unopposed action of the peroneal innervated musculature is not present. Hence, the walking track shows an increased print length, decreased toe spread, and decreased intermediate toe spread without the tendency of foot eversion. Owing to the loss of the peroneal nerve function, there is a more abnormal print with evidence of toe dragging and a more slurred print [1].

HISTORY OF SCIATIC INDEX FORMULA

Prior to de Medinaceli et al. [10], gait analysis had been described comprehensively by Hruska et al. [19, 20]. However, de Medinaceli's group [10] was interested in an assay of the end result of neurological function in contrast with electrophysiological recordings of conduction velocity or amplitude, and with morphometric analysis of nerve fibre numbers or axon-myelin ratios. Furthermore, de Medinaceli's group [10] was interested in an assay they could apply to a model of localized severe nerve injury. Therefore, they incorporated the parameters that directly measured from the rat's footprints: TOF (distance to opposite foot), PL (print length), TS (toe spread), ITS (intermediate toe spread), angle of feet, and width between feet and toe. But, they selected four variables, TOF, PL, TS, and ITS for calculation of the index formula. The TOF (the swing of the opposite limb) measures the capacity of the experimental limb to support the animal's weight. TS and ITS, indicators of condition of the peroneal nerve, were based on previous studies [3, 15, 18]. They found the PL to be short in normal animals that walk only on their toes whereas animals with nerve damage place the whole foot on the ground and sometimes even drag their toes. De Medinaceli et al. [10] gave equal importance to the different components in the index formula (Fig. 2A). In 1986, Carlton and Goldberg [5] eliminated from the formula the variable relating to distance to the opposite foot (Fig. 2B). Later, in 1989, Bain et al. [1] reported that the indices of sciatic function, as described by De Medinaceli et al. [10] and Carlton and Goldberg [5], led to values that were not indicative of the nerve lesions created. Bain et al. [1] provided indexes for the three nerve functions (sciatic, posterior tibial, peroneal) that were statistically, not empirically, derived. Indices for a sciatic, peroneal, and posterior tibial function index are created based on the coefficients

A. De Medinaceli, Freed and Wyatt, 1982

$$SFI = \left[\left(\frac{ETOF - NTOF}{NTOF}\right) + \left(\frac{NPL - EPL}{EPL}\right) + \left(\frac{ETS - NTS}{NTS}\right) + \left(\frac{EIT - NIT}{NIT}\right)\right]\frac{220}{4}$$

B. Carlton and Goldberg, 1986

$$SFI = \left[\left(\frac{NPL - EPL}{EPL}\right) + \left(\frac{ETS - NTS}{NTS}\right) + \left(\frac{EIT - NIT}{NIT}\right)\right]\frac{220}{3}$$

$$TFI = 125\left(\frac{NPL - EPL}{EPL}\right) - 43.8\left(\frac{ETS - NTS}{NTS}\right) + 252\left(\frac{EIT - NIT}{NIT}\right)$$

$$PFI = (2 \times SFI) - TFI$$

C. Bain, Machinnon, and Hunter, 1989

$$SFI = -38.3\left(\frac{EPL - NPL}{NPL}\right) + 109.5\left(\frac{ETS - NTS}{NTS}\right) + 13.3\left(\frac{EIT - NIT}{NIT}\right) - 8.8$$

$$TFI = -37.2\left(\frac{EPL - NPL}{NPL}\right) + 104.4\left(\frac{ETS - NTS}{NTS}\right) + 45.6\left(\frac{EIT - NIT}{NIT}\right) - 8.8$$

$$PFI = 174.9\left(\frac{EPL - NPL}{NPL}\right) + 80.3\left(\frac{ETS - NTS}{NTS}\right) - 13.4$$

Figure 2. Index formulas; **A.** Index formula described by De Medinaceli, Freed, and Wyatt [10]; **B.** Index formula described by Carlton and Goldberg [5]; **C.** Index formula described by Bain, Mackinnon, and Hunter [1]; SFI — sciatic function index, PFI — Peroneal function index, TFI — tibial function index.

derived from multiple linear regression analysis. They suggested a new modification of the SFI, calculating the factors as follows: print length factor (PLF); toe spread factor (TSF); and intermediary toe spread factor (ITF). These factors were then incorporated into the Bain-Mackinnon-Hunter sciatic function index formula (Fig. 2C). A similar set of sciatic nerve indices was developed in mice [21]. Inserra et al. [21] reported high correlation for SFI with PL and TS, for peroneal function index with TS, and for posterior tibial index with PL in mice. By these observations, they constructed an index formula based on weighted contributions of the components of the sciatic function index.

SOME PROBLEMS IN OBTAINING WALKING TRACKS

Sometimes it is difficult to obtain clear print marks. The reported difficulties are as follows.

Long print length

One of the most difficult points to determine is that for the heel. When a rat is first placed in the corridor, it may remain still, pressing the entire footpad and hell down, creating a very long print length but not a walking print. At the end of the walkway, before entering the dark box, it might put all its weight onto its hind legs, again creating a very long print [12]. To discard this behaviour, the rat should first be allowed two or three conditioning trials, during which it can stop to explore the walking pathway. After these trials, the rat should walk steadily to the darkened cage [37].

Autotomy

After transection of the sciatic nerve, rodents frequently scratch and bite their anaesthetised foot, resulting in amputation of one or more toes (especially the last two digits). This is termed autotomy or autophagy. This phenomenon was first described and named by Wall et al. [39]. Mice show autotomy very similar to that seen in rats but the onset is somewhat faster [39]. Autotomy is usually seen in the beginning of the third postoperative week. Autotomy starts with nibbling of toenails (Fig. 3) and then extends progressively to the toes and feet (Fig. 4). Subsequently, infection and oedema may start in the attacked regions. The extent of autotomy is scored according to the scale used by Wall et al. [39]. Briefly, one point is tallied for the loss of one or more toenails, and an additional point is scored for each one-half toe amputated, and for a total score when all toes are removed.

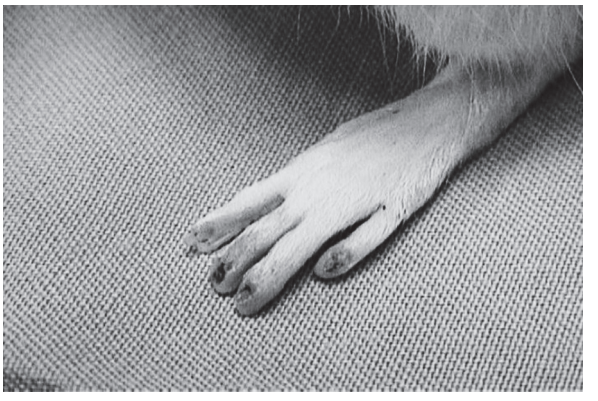

Figure 3. Nibbling of toenails.

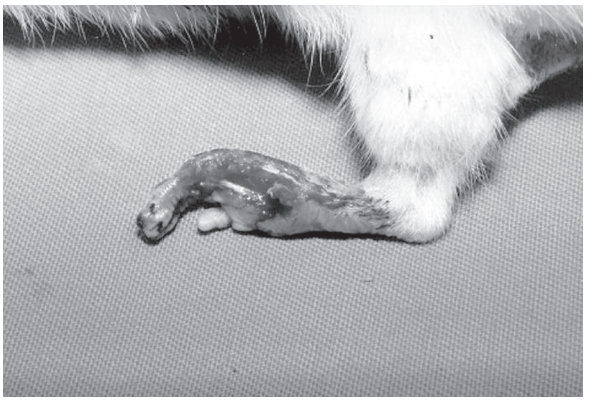

Figure 4. Appearance of severe autotomy.

Although it has been suggested that this behaviour is simply an effort to shed an insensate appendage, several researchers have attributed it to the animal's response to a painful condition that it perceives as arising from the denervated body part, named anaesthesia dolorosa. The painful perception arising from the injured nerve may originate from impulses spontaneously generated in the regenerating axonal sprouts because of mechanical compression within the neuroma [8, 39].

When these rats or mice are part of a study using the sciatic function index, autotomy results in unusable data, since the necessary foot marks have been removed. Therefore, in most cases where autotomy occurs the hind limb can no longer serve as the site at which nerve repair can be studied. For the prevention of this problem, a deterrent in the form of a foul-tasting substance [34] or some chemical substances [2, 24, 31] have been used with beneficial results. This behaviour can be significantly limited when housing male rats with females [43].

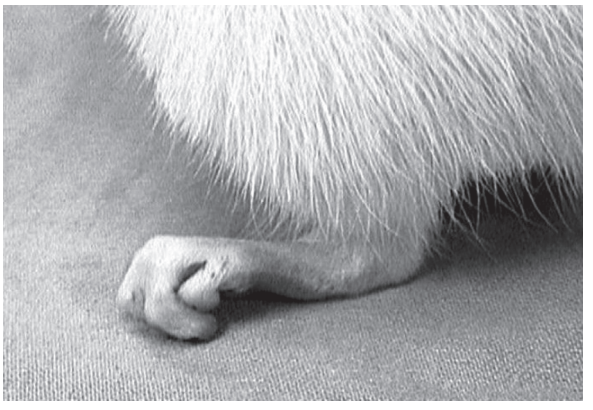

Figure 5. Appearance of contracture formation.

It would be helpful, therefore, to be familiar with the phenomenon of autotomy and know which rats are least likely to mutilate themselves. It is reported that female Sprague-Dawley rats are significantly less likely to perform autotomy than males [40]. In contrast to Weber et al. [40], Carr et al. [6] mentioned that Lewis rats have been demonstrated to exhibit the least autotomy.

Contracture formation

Sciatic and peroneal nerve injuries often cause joint contractures such that the rats use the dorsum of the affected foot (Fig. 5). Tibial nerve injuries cause some rats to bear weight on the medial aspect of the foot with the fifth toe elevated [17]. The formation of flexion contracture may occur due to a faster or more complete reinnervation of the flexor muscles in comparison with the extensor muscle group [7]. Contractures may also have contributed to the unexpected findings of a decline in the mean SFI. Contracture formation can be seen not only in rats but also in mice. The incidence of contracture formation in mice [42] is similar to that reported for rats [17]. As a result of contracture formation, it is difficult to measure the print length. To solve this problem, Chamberlain et al. [7] developed a new method to measure the print length in the presence of flexion contracture after sciatic transection, whereby the sum of the distance from the heel to the proximal knuckle on the print and the distance from the proximal knuckle to the end of the toe is calculated. To prevent the development of flexion contractures, the injured leg must be exercised manually on a weekly or biweekly basis, or a wire mesh must be used, where the animal is allowed to play freely, to provide continuous physiotherapy throughout the period of denervation [25]. Daily physical activity has a positive influence in the early phase of nerve regeneration, including motor and sensory function [33, 36], as would be provided in real clinical situations [42].

MATERIALS USED TO OBTAIN TRACKS: THEIR ADVANTAGES AND DISADVANTAGES

An overview of the literature shows that in some experiments, the bottom of the track was lined with various kinds of materials, or the rat's hind feet were dipped or painted with various substances, in order to refine and improve the prints for walking track analysis.

De Medinaceli et al. [10] used an X-ray developer and film to observe the prints. Prior to Medinaceli's group, attempts to record the rat's footprints for gait analysis used Vaseline and white paper [32], or grease and polygraph chart paper [19, 20]. These techniques produce prints subject to error regarding the actual anatomy of the rat plantar surface. A complex technique requiring dye staining of paper has been reported by Lowdon et al. [27], in which water is utilized to produce a blue track image on yellow brown paper. Johnston et al. [22] suggested that the paint and paper method had many advantages over the original method of X-ray developer and film. The reported advantages are as follows: paper is more readily available than x-ray film; it is easier to cut and provides better traction; paint is a non-toxic agent and can be washed easily; the rat's feet are not chronically exposed to potentially caustic developer; slippage and print smearing are kept to a minimum; it is easy to visualize the paint of the plantar surface before the rat walks so that all the important anatomical structures will be imaged.

Westerga and Gramsbergen [41] introduced the use of a mirror to obtain two views of the rat's hind paw, the plantar and the side-view. A video recording technique to measure SFI was reported by Walker et al. [38] and Dijkstra et al. [13]. The rats are placed in a Perspex runway, and a single mirror placed at an angle of 45° below the animal, being filmed from the side. Each frame of the video image is selected from a non-hesitant step. The video analysis of standing was described by Bervar [4], to introduce a new functional loss index, in static conditions: the static sciatic index (SSI).

CONCLUSIONS

Standardization of track analysis will be essential in interlaboratory comparisons of data. While most reports have specified the Sprague-Dawley rat, it is reemphasized that the normative data should not be applied to other rat strains; rather, each laboratory should obtain normative data for the strain of Rattus norvegicus, such as Wistar or Lewis. We suggest that verification of SFI with other modified index formulas is important prior to use of these functional indices for rat strains available in the researcher's laboratory.

The use of walking track analysis provides a noninvasive method of assessing the functional status of the sciatic nerve during the regeneration process. Because proper walking requires coordinated function involving sensory input, motor response, and cortical integration, SFI may therefore be better than simply using basic electrophysiology and histomorphometry of axon growth and muscle reinnervation, if the research focus concerns functional outcome.

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