Complications and Effects of Dorsal Root Ganglion Stimulation in the Treatment of Chronic Neuropathic Pain

A Nationwide Cohort Study in Denmark

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Complications and Effects of Dorsal Root Ganglion Stimulation in the Treatment of Chronic Neuropathic Pain: A Nationwide Cohort Study in Denmark.

Running head:

DRG stimulation: Effects and complications.

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Dr. Horan assisted with the acquisition of data, data analysis, drafting the article, and revising the article. Dr. Jacobsen assisted with the acquisition of data and drafting the article. Dr. Scherer assisted with the concept and design of the work, acquisition of data, interpreting data, and revising the article. Dr. Rosenlund assisted with the concept and design of the work, acquisition of data, interpreting data, and revising the article. Dr. Gulisano assisted with the acquisition of data and revising the article. Dr. Søe assisted with the acquisition of data and revising the article. Prof. Sørensen assisted with the acquisition of data, managing data via the Neurizon database, and revising the article. Dr. Meier assisted with the acquisition of data, managing data via the Neurizon database, and revising the article. Dr. Blichfeldt-Eckhardt assisted with the concept and design of the work,

acquisition of data, data analysis, interpreting data and revising the article. All authors discussed the results and commented on the manuscript.

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Dr. Jacobsen: Boston Scientific (travel and conference fees).
Dr. Gulisano : Boston (travel support), Abbott (travel support), Medtronic (teaching fee, travel support and proctoring fee).
Prof. Sørensen : Neurizon (co-ownership).
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Dr. Blichfeldt-Eckhardt: Abbott (course and travel fees), Boston Scientific (course and travel fees), Medtronic (course and travel fees).
Dr. Scherer: Abbott (travel and conference fees), Boston Scientific (travel and conference fees), Medtronic (travel and conference fees).
Dr. Rosenlund: Abbott (travel and conference fees), Boston Scientific (travel and conference fees), Spinal Modulation (travel and conference fees).
The remaining authors declare no conflicts of interest.

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Abstract

Objectives

Dorsal Root Ganglion (DRG) stimulation is a novel treatment of chronic neuropathic pain and has been shown to be efficacious across several case reports and randomized trials. However, long-term follow-up is limited, as are reports of complication rates. This study presents efficacy and complications for patients treated with DRG stimulation.

Materials and Methods

We performed an observational, multicenter cohort study of all patients in Denmark implanted with FDA-approved DRG stimulation systems to treat chronic, neuropathic pain between 2014 and 2018. Follow-up period was 1-3 years.

Results

Forty-three patients underwent trial DRG stimulation; 33 were subsequently fully implanted. Pain location: 58% lower extremity; 21% upper extremity; 21% thoracic/abdominal. At the end of the observation period, 58% of fully implanted patients were still implanted; 42% had fully functional systems.

In these patients, average Numerical Rating Scale (NRS)-score of pain was reduced from 6.8 to 3.5 (p=0.00049) and worst NRS-score was reduced from 8.6 to 6.0 (p=0.0039) at 12 months follow-up. Pain Catastrophizing Score was reduced from 32 to 15 (p=0.0039).

Thirteen patients experienced complications related to defect leads (39% of implanted systems). In 4 patients (12%) lead removal left fragments in the root canal due to lead

fracture, and 3 patients suffered permanent nerve damage during attempts to replace broken leads.

Conclusions

This study suggests a significant, clinically relevant effect of DRG stimulation on neuropathic pain, but also demonstrates substantial problems with maintenance and revision of currently available systems. Consequently, treatment with equipment marketed specifically for DRG stimulation is currently paused in Denmark.

Key words: Neuromodulation, DRG stimulation, chronic pain, efficacy, complications

1.0 Introduction:

Dorsal root ganglion (DRG) stimulation is a recent development in the treatment of chronic, neuropathic pain, but evidence of long-term effect, in particular, is still limited and the rate and extent of complications is uncertain. The DRG is a potentially attractive therapeutic target. The DRG holds the cell bodies of the primary sensory neurons, which process and transmit sensory signals from the periphery to the central nervous system and are implicated in the development and maintenance of chronic neuropathic pain[1]. The DRGs are located within or close to the intervertebral foramina[2,3] where it can be a target for neuromodulation and accessed via several routes[4-6].

DRG stimulation is an alternative to spinal cord stimulation (SCS) and has several proposed advantages. First, it can confine stimulation to a smaller, more specific area, thereby minimizing the risk of unwanted paresthesia outside the painful area[7]. Second, it may provide stimulation in areas that can be difficult to cover with SCS such as very distal extremity areas or the torso[1,6,8]. Third, DRG stimulation is less affected by postural changes and may thereby produce a more stable stimulation[9]. Fourth, DRG stimulation can often be effective even with amplitudes below the paresthesia threshold, and may thus produce less paresthesia, which is preferable in some individuals[7,9].

While the randomized ACCURATE trial showed DRG stimulation to be efficacious and safe compared to SCS[9], evidence for the long-term effect of DRG stimulation is still limited and mostly confined to case reports[10-19]. Studies that do include long-term follow-up

report relevant pain relief in 42-82% of cases[6,9,20-23]. Complication rates are unclear and rarely reported[20,21,24], but a recent database study indicates that complications are not uncommon and about half (47%) are device-related[25]. A second recent report[26] using manufacturer safety and complaint records found adverse event rates in 3% of records, and compared these rates directly and favorably to the adverse event rates in the ACCURATE trial[9]. This discrepancy highlights the need for further studies using real-world evidence; specifically, complete datasets on long-term efficacy and complication rates from common clinical practice.

The aim of this study was to explore long-term effect and complication rates of DRG stimulation during a five-year period on a national scale in Denmark.

2.0 Materials and Methods:

2.1 Design and patients

This observational, multicenter cohort study was approved by the Danish Data Protection Agency. The study was purely observational and all patients received usual standard of care. Therefore, in accordance to Danish regulations, the study was not processed by the regional ethics committee. Informed, written consent was obtained from all patients. The participating centers included the neurosurgical departments at three Danish University Hospitals: Center 1: Odense University Hospital; Center 2: Aalborg University Hospital; Center 3: Aarhus University Hospital.

This cohort includes all patients in Denmark who were implanted with neuromodulation systems specifically marketed and FDA-approved for DRG stimulation. This includes both trial implants and full implants (Figure 1; additionally, see section 2.2 below). Implantations were done in the period 2014 and 2018. Patients were selected for DRG stimulation if they were diagnosed with localized, neuropathic pain in the distal extremities or on the truncus if the pain was confined to 1-2 dermatomes. The patients had pain location as follows: 58% lower extremity; 21% upper extremity; 21% thoracic/abdominal. At Center 1, all patients were screened with individualized transcutaneous electrical nerve stimulation (TENS) in the pain area, and only patients with pain reduction during TENS treatment (individually assessed by the implanting doctor based on the patient's feedback) were considered for DRG implantation. Patients were not considered for implantation in case of pregnancy, structural

diseases in the central nervous system, malignant disease, complex psychiatric illness, dementia or other cognitive disability, alcohol, or substance abuse.

2.2 Implantation

At Center 1 and 2, patients were analgosedated with Remifentanil 50 µg/ml or Fentanyl/Alfentanil and Propofol in an individualized dose, and received local anesthesia (Lidocaine or Ropivacaine). At Center 3, patients were sedated with a low-dose infusion of propofol supplemented with fentanyl and alfentanil, and local analgesia was performed with a 1:1 mixture of lidocaine 1% with adrenaline and Ropivacaine 0.5%.

The DRG leads (Axium™, produced by Spinal Modulation, now Abbott, USA) were introduced to the epidural space via a Tuohy needle at the level of the target foramen or the level below. It was placed at the relevant level under fluoroscopic guidance, with the four lead contacts in the intervertebral foramen along the dorsal spinal nerve root and the DRG. An intraoperative stimulation test was performed and 1-3 leads were placed in accordance with the target dermatomes and the patient's feedback to this "on table trial". Once adequate paresthesia coverage of the painful area was obtained, a lead loop was created epidurally under x-ray control and as trained at implantation technique courses. The lead was fixed to the fascia with a silicone anchor to prevent lead migration. Special care was taken to ensure that epidural space loops on the lead were sufficiently placed during the original implants. The DRG lead implantations were in all cases performed according to the procedure recommended by the manufacturer. At Center

1, the leads were tunneled externally using a temporary extension cable and connected to a test device, and patients underwent a one-week trial stimulation (undergoing prophylactic antibiotic treatment with dicloxacillin). Based on the patient's feedback, the implanting physician assessed the level of pain relief in response to trial stimulation in a clinical evaluation. If this was assessed as adequate, the patient went on to full implantation. If not, the leads were explanted (Figure 1). Ten patients received a full primary implantation without the one-week trial because of convincing effect of the "on table trial". At Center 2, all patients underwent one week of trial stimulation. At Center 3, all patients were implanted based on the "on-table trial".

All procedures were performed by surgeons with extensive experience in SCS implantation techniques. At Center 1 and 2, surgeons had furthermore completed at least 2 days of rigorous training in DRG implantation techniques before starting the procedure in their facility. At Center 3, an implanter with extensive experience in DRG-implantations from a foreign center was invited to supervise the procedures.

2.3 Data collection and follow-up.

At Center 1, DRG-implantations were performed between January 2014 and November 2016 and the observation period was ended in January 2018. At Center 2 and 3, DRG-implantations were performed between November 2016 and February 2018 and study the observation period was ended in March 2019. Observation period is defined as the end of data acquisition for the purpose of the present study, but patients are continually and routinely followed in their local

out-patient setting. As such, all patients had at least one year of follow-up in the context of this study. All patients were registered in the Neurizon database[27]. The Neurizon database contains "detailed patient characteristics and core treatment parameters, including procedure-related details and complications" across multiple European countries for the "everyday clinical use, research, and quality assurance within the neuromodulation field"[28]. Baseline demographic data was registered before the operation and patients completed a paper questionnaire at baseline and at 3, 6, 12, 24, and 36 months after the operation, depending on individual follow-up duration. The questionnaire included ratings of pain intensity (primary outcome) during the previous 7 day period (worst and average pain) on a 0-10 numerical rating scale (NRS) and the Pain Catastrophizing Scale (PCS)[29], the Major Depression Inventory (MDI)[30], and the 36-Item Short Form Health Survey (SF-36) as secondary outcomes. Patients were routinely seen on the first postoperative day as well as 3, 6, 12, 24 and 36 months after the operation in an out-patient setting for the purpose of evaluating the treatment and to adjust the programming of the implantable pulse generator (IPG), if necessary (At Center 2, the 3-month follow-up was carried out by the patient's primary care physician). In case of problems or complications to the treatment, the patients were seen more often.

2.4 Statistical analysis.

For each of the outcomes (NRS, PCS, MDI, SF-36) we present a pre-post analysis at baseline and at 12-month follow-up. Additionally, we present a time series of all encounters at all pre-

defined follow-ups. For pre-post analyses, paired non-parametric Wilcoxon signed rank-tests were performed. To correct for multiple comparisons across primary and secondary outcomes (n=12: average NRS, worst NRS, PCS, MDI, and each category of SF-36), we took a conservative approach using Bonferroni correction and compared the p-value of each test against $\alpha=0.05/12$. As such, efficacy outcomes were considered statistically significant at $p < 0.0042$. All statistical tests were carried out in MATLAB 2014b (Mathworks, Natick, Mass, USA). Complications are presented as counts and percentage of implanted systems.

3.0 Results

From January 2014 to February 2018, 43 patients were selected for DRG-treatment as presented in Figure 1 (32 patients from Center 1; 8 patients from Center 2; 3 patients from Center 3). While 33 patients were fully implanted, only 19 patients (58 % of implanted patients) were still implanted at the end of the observation period (range: 1-3 years). Of these patients 14 (42% of implanted patients) had fully functional systems, and 5 had partially functional systems with some leads being defect at the end of the observation period. Demographic data are presented in Table 1.

The combination of baseline and one-year follow-up data was available in 16 of the 19 patients who were still implanted at the end of the observation period (data missing from one patient from each of the 3 centers). There were no meaningful differences in outcomes or complication rates amongst patient from the different centers. Data from the explanted patients were too incomplete to contribute to meaningful analysis. We therefore focus our analyses of the efficacy of DRG stimulation on those patients who are still being treated with the system.

3.1 Effects

For the patients still implanted at the end of the observation period (n=16), average pain NRS during the past 7 days (Fig. 2A left panel) was reduced from mean 6.8 (s.e.m. = 0.35) at baseline to 3.5 (0.68) at 12 months follow-up (2-sided paired Wilcoxon signed rank test, W=103, p=0.00049) while maximum NRS during the past 7 days (Fig. 2A right panel) was reduced from

8.6 (0.33) at baseline to 6 (0.81) at 12 months (W=64, p=0.0039). Figure 2B shows the development in NRS-score during a 3-year follow-up period, which indicates that the reduction in NRS was stable over time.

Data on the secondary outcomes was limited as only 10 of the 19 patients, who were still implanted after the end of the observation period, completed the 12-month questionnaires, and only 8 patients completed all 3 questionnaires. Among these patients, however, Pain Catastrophizing Score (Fig. 3A left panel, n=9) was significantly reduced from 32 (4.1) at baseline to 15 (3.1) at 12 months follow up (p=0.0039), while no significant changes was observed in MDI (Fig 3B, n=8) or SF-36 scores (Fig 3C, n=10). Right-hand panels of Figure 3A-C shows the development secondary outcomes during the 3-year follow-up period, which indicates that the trends at 12-month follow-up were stable over time.

3.2 Complications

The most frequent complications were hardware-related and included broken and migrated leads (Figure 1 and Figure 4). Thirteen patients had one or more defect leads (39% of implanted systems). Of these, 11 cases were confirmed to have fractures, which occurred at the anchor, the implantable pulse generator (IPG), or in one of the loops (Figure 5A-B). The remaining 2 cases had loss of paresthesia and pain-relieving effect in addition to high impedance, which indicated lead fracture, though the leads were not examined further during revision. Five patients were found to have migration of leads. In 2 of these cases, implanters had elected not to anchor the

leads due to previous fracture in relation to the anchor, leading to subsequent migration. Except these two cases, anchors were used in all other implantations.

The median time from implantation to explantation was 413 days (n=14; interquartile range = 237 to 665 days).

Two patients, whose systems were explanted due to migrated leads (Figure 1) had previously experienced several revisions caused by broken leads, and both therefore refused further revisions and were explanted.

In 4 patients (12% of implanted systems), it was not possible to remove the entire lead during revision. The lead broke during removal, leaving the tip with one or more metal parts in the root canal or epidural space (Figure 6A). As shown in Figure 6B, one lead was removed with considerable amounts of scar tissue debris, illustrating the risk of the lead getting stuck in the root canal. In 7 patients, replacement of broken leads was not possible due to either obstructive lead fragments or scar tissue. In 3 patients, persistent or repeated attempts to replace leads resulted in permanent nerve damage. These included 2 cases of damage to the nerve root, resulting in increased neuropathic pain, and 1 case of medullary damage resulting in new neuropathic pain, tetraparesis, and bladder dysfunction. Finally, 3 patients were explanted because of loss of or substantial waning of effect, and 1 patient experienced slight worsening of pain after implant in spite of a successful trial period.

4.0 Discussion

In this study, we present data from all patients implanted with neuromodulation systems specifically marketed and FDA-approved for DRG stimulation, in Denmark from 2014-2018. We demonstrate a significant and clinically relevant effect of DRG stimulation on neuropathic pain, while also demonstrating substantial problems with the maintenance and revision of the currently available systems.

The treatment resulted in almost 50% reduction in pain score 12 months after implantation in the subgroup of patients, who were still implanted at the end of the observation period. This effect size is comparable to previous studies of DRG stimulation[6,9,22]. Further, we observed that this reduction was consistent over time. We also observed a significant reduction in pain catastrophizing score, which is also supported by similar cohort studies[20,21]. There were no significant changes in MDI or SF-36 score in the subgroup that completed the questionnaires.

However, the treatment was substantially impeded by problems related to maintaining and revising the system. This is an area which has previously received limited attention in studies of DRG stimulation. One review summarizing the field defined safety summaries in only 3 of 12 included studies[24]. Recent conflicting reports have retrospectively queried databases (using a directly supplied, manufacturer database[26], or the FDA's Manufacturer and User Facility Device Experience[25]) to evaluate the safety of DRG stimulation. Their estimates of adverse event are discrepant, particularly on lead migration and lead fracture[31,32], which were major contributors to complications in our cohort. The prospectively

collected complications-data in our cohort contribute to this debate of long-term safety of DRG stimulation (in addition to its long-term efficacy). In our study, the frequency of lead fractures was considerably higher than we usually observe with spinal cord systems (which for many patients would be an alternative). We are not reporting a direct comparison of SCS to DRG stimulation, but both the high number of adverse events, and our observation that rates of adverse events were higher in the present DRG cohort than in our SCS patients, is counter to previous reports. For example, the ACCURATE trial directly compared SCS to DRG stimulation trial and found "the rates of [serious adverse events] were 10.5% (8/76) in the DRG arm and 14.5% (11/76) in the SCS arm"[9]. Similarly, the problems relating to revisions of dysfunctional systems were greater than we usually observe with spinal cord systems. While a rigorous test of the leads' physical properties is outside the scope of this study, it was our observation that, over time, the texture of the leads changed: being softer, smoother, and more flexible than usual SCS-leads at the time of implantation, they became considerably stiffer at explantation, which possibly facilitated their tendency to break. As a response to the lead breakages, we were advised by the manufacturer to not anchor the leads, and to instead solely depend on epidural loops as fixation. However, the leads did not only break at the anchor and we observed increased tendency for lead migration of unanchored leads. For these reasons, this did not present a solution in our hands.

Another serious challenge was our difficulty revising the systems. We had several cases of leads breaking during removal, resulting in lead parts being lost in the root canal of the

afflicted patient. First, this presented a mechanical block for replacement of a broken lead in case of otherwise effective treatment response. Second, it would impede future MRI-scans. Third, any long-term adverse consequence of metal debris left (as opposed to leads being placed) in the root canal is to our knowledge not studied. Another impediment to the replacement of broken leads was an apparent tendency for the development of fibrosis in the root canal after the primary implant. The result was that previously effective treatments could not be reinstated after revision of the system, which caused considerable distress to the patients. In three such cases of difficult revisions in patients (with otherwise extensive effect of the stimulation), persistent attempts to replace the lead resulted in permanent neural damage.

Partial follow-up is a significant limitation in this study. The outcomes related to efficacy are based on a relatively small sample size (those still implanted at the end of the observation period), and yet we did not have complete data on all participants. Incomplete follow-up was substantial for the questionnaires, which introduces a report bias for our secondary effect parameters. These should therefore be interpreted with caution. And as noted above, we only present efficacy data on the patients, who were still implanted at the end of the study period. If explanted, the patient is no longer routinely followed in the out-patient setting (unless for other treatment not related to DRG stimulation). It is important to note that incomplete data as a result include both patients, who were explanted due to lack of effect, and patients with positive treatment effect, who were explanted due to lead dysfunction and were not possible to re-implant.

Crucially, the data on complications were complete and included all patients who received DRG stimulation in Denmark during the observation period. This was possible due to ongoing national commitment of data into the Neurizon database. As such, this provides real-world evidence to compliment the retrospective database survey of DRG stimulation safety[25,26], and because all implanted patients are included, this cohort is particularly suitable to detect complications.

It could be argued that complication rates may be lower in centers with high volume of implants. This is indeed possible. Comprehensive and complete follow up data on complications from additional centers is needed, if possible comparing centers with high and low volume of implants with otherwise similar setups. The association between volume of surgeries, both by hospital and within surgeon, and survival outcome has been repeatedly studied and debated, and tends toward a positive correlation with a small effect size[33], but varies markedly with the specific procedure[34]. Associations between volume and complications are less well understood, but e.g. length of stay and readmission rates (measures of resource use) are not associated to volume[35] with few studies of this association in the neuromodulation literature. These show heterogenous effects[36,37]. In our study, most of the complications we observed occurred in patients with successful implantation and up to several years of successful treatment, arguing against technical or implantation-related issues. Rather, it appears that complications were related to apparent changes to leads and local tissue transformations, which may

accumulate over time, resulting in late complications. The center with only three implants had invited a foreign, experienced implanter from a high-volume center to supervise the procedures.

5.0 Conclusion

DRG stimulation presents an effective method to relieve peripheral neuropathic pain, but is impeded by limited long-term stability of the available systems. In Denmark, the treatment with equipment marketed specifically for DRG stimulation has currently been put on hold. It is the consensus among Danish implanters that the rate of system failures is too high, and the possibilities of performing reliable revisions of the systems are too limited.

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Legends:

Figure 1. DRG stimulation treatment over time.

Forty-three patients underwent trial implantation, and 33 of these were fully implanted. Fourteen were explanted during study follow-up. Nineteen patients were still implanted at the end of the observation period. Of these, 5 have only partially functional systems.

The light blue textbox highlights those patients, who are still implanted and are included in the analyses of effects of the treatment.

The dark blue textboxes highlight those patients, who have experienced complications as described in the results section.

The horizontal gray dashed line indicates the end of the observation period. Patients are still followed as part of normal clinical routine.

[a]Patients with defect leads were not re-implanted either because lead parts left in the targeted root canal made this impossible; because they had undergone repeated revisions; or because of patient refusal.

[b]Patients who were explanted due to migrated leads refused re-implantation because of repeated revisions to the system.

Figure 2. Average and worst pain scores.

2A: Pain score, NRS=numerical rating scale score at baseline and after 12 months. Left panel: average NRS-score of past week. Right panel: worst NRS-score of past week.

2B: Development of NRS-score over time. It is important to note that the number of patients with responses (n) is reduced over time, and n at each time point is indicated at the top of the panel. Scores of individual patients are indicated with gray circles.

Left panel: average NRS of past week. Right panel: worst NRS of past week.

Figure 3. Secondary outcomes.

3A: PCS=Pain Catastrophizing Scale score at baseline and after 12 months (left panel) and development in PCS-score over time (right panel). Same conventions as in Figure 2.

3B: MDI=Major Depression Inventory-score at baseline and after 12 months (left panel) and development in MDI-score over time (right panel). Inset of left-hand panel shows the number of patients in each of 4 depression severity categories predefined for MDI. Same conventions as in Figure 2.

3C: SF-36=Short Form 36-score at baseline and after 12 months (left panel) and development in SF36-score over time (right panel). Gray bars indicate baseline with each subsequent colored bar showing score at 3, 6, 12, 24, and 36 months.

Figure 4: Complications to DRG stimulation.

Number of patients (n) with complication by category. Percentages are of fully implanted systems (see Figure 1).

The two infections were subcutaneous infections at the implanted pulse generator (IPG)-pocket.

Figure 5. Examples of lead fractures.

5A: Broken lead. 46-year-old female, treated for neuropathic abdominal pain syndrome with almost complete pain relief. Revised due to two broken leads.

5B: Broken lead. 59-year-old male, treated for neuropathic pain in the foot and lower leg. Lead broke 2 years after implantation. It has not been replaced because of risk of lead breakage during removal, and contacts are left in the root canal as a result. The patient has one functioning lead and therefore partial pain relief.

Figure 6. Examples of dysfunctional leads.

6A: Lead tip, with 4 contacts left in the patients epidural space and root canal. 48-year-old male, treated for neuropathic pain in the left arm. Revised due to dysfunctional stimulation. Lead broken during revision. The patient has part of the painful area covered by the remaining lead.

6B: Lead with adhering scar tissue. Same patient as fig. 5A.

Table 1. Patient demographics.

Variable	Patients for trial	Implanted patients
Number of patients	43	33
Age, years (SD)	43 (10)	42 (10)
Sex, female (%)	11 (26%)	9 (27%)
Months with pain pre-implantation (SD)	80 (66)	71 (63)
Number of leads (SD)	1.5 (0.8)	1.7 (0.7)
Area of pain (%)		
Arm/hand	9 (21%)	5 (15%)
Thorax/abdomen	9 (21%)	8 (24%)
Leg/foot	25 (58%)	20 (61%)

Table 1

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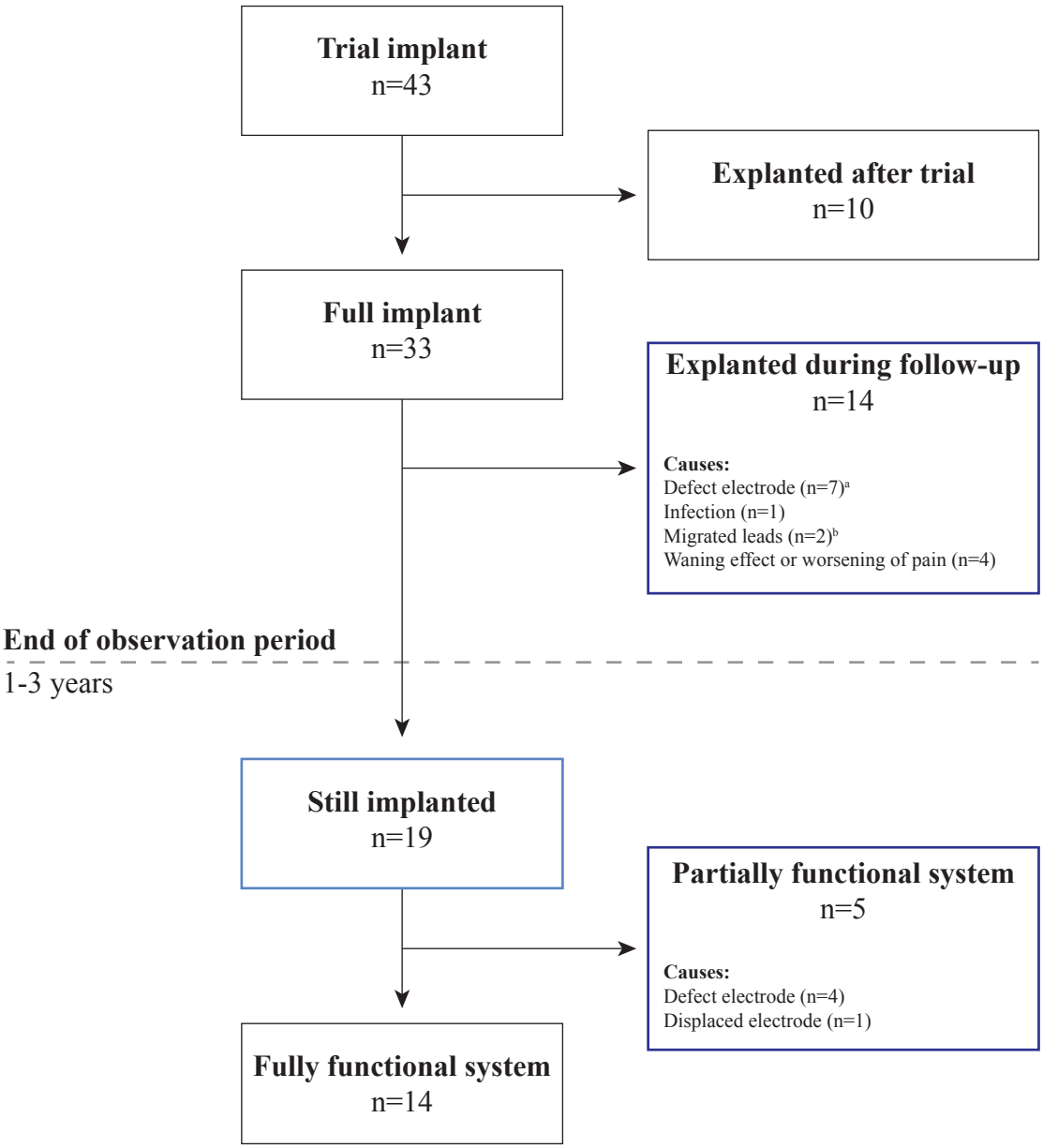

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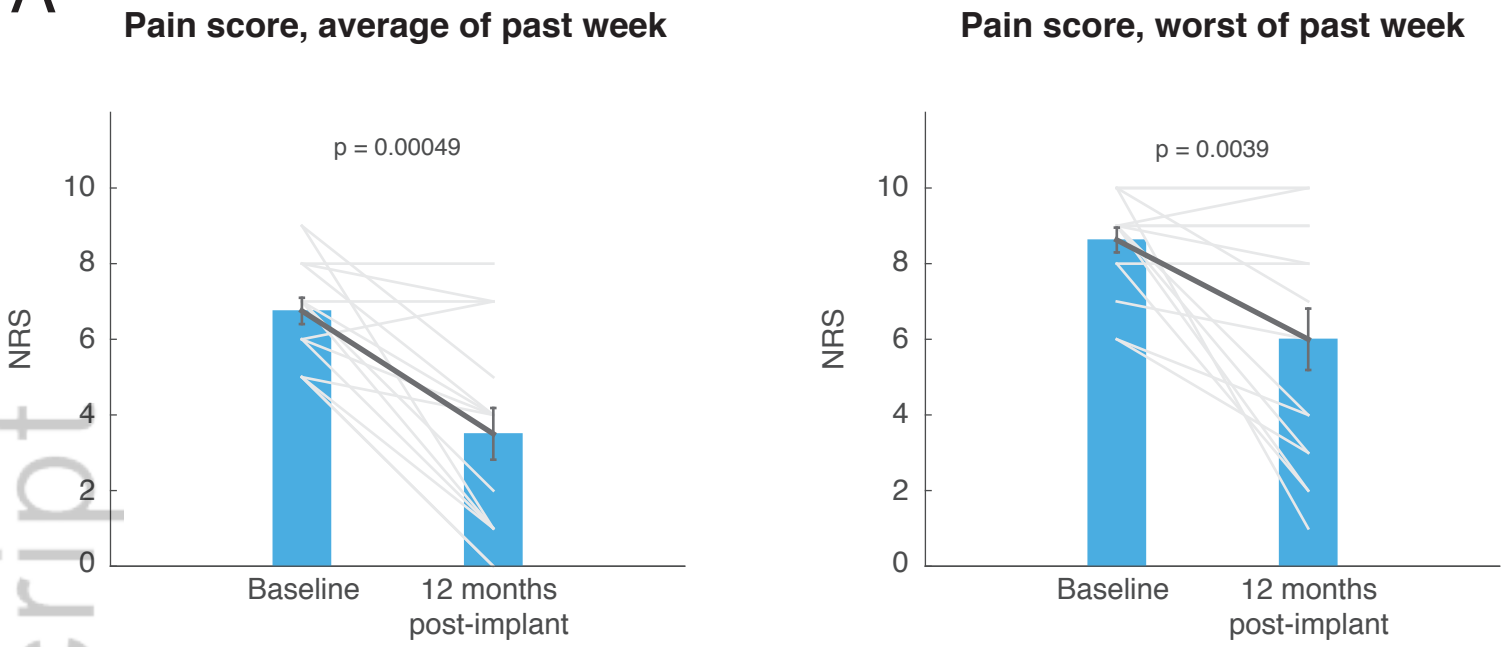

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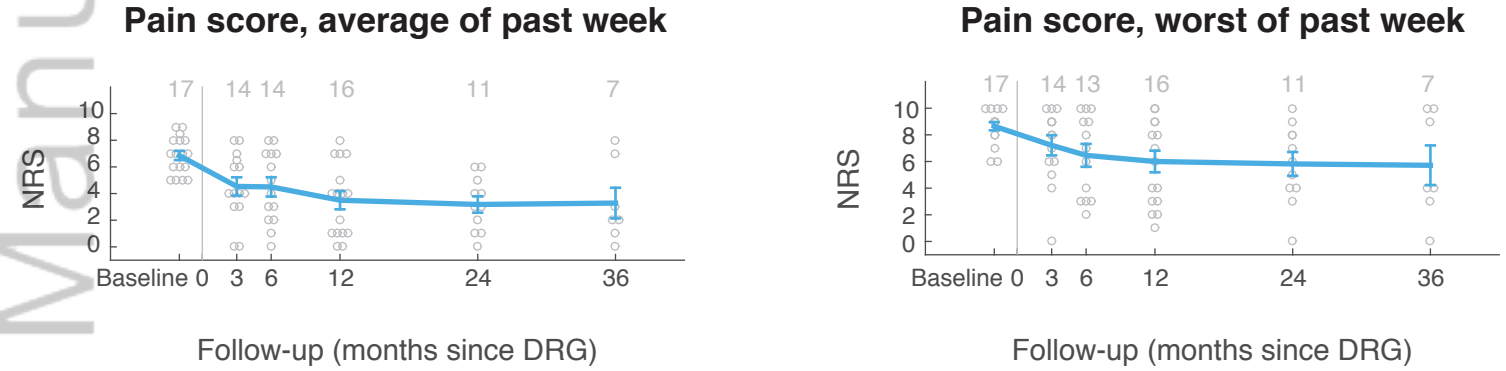

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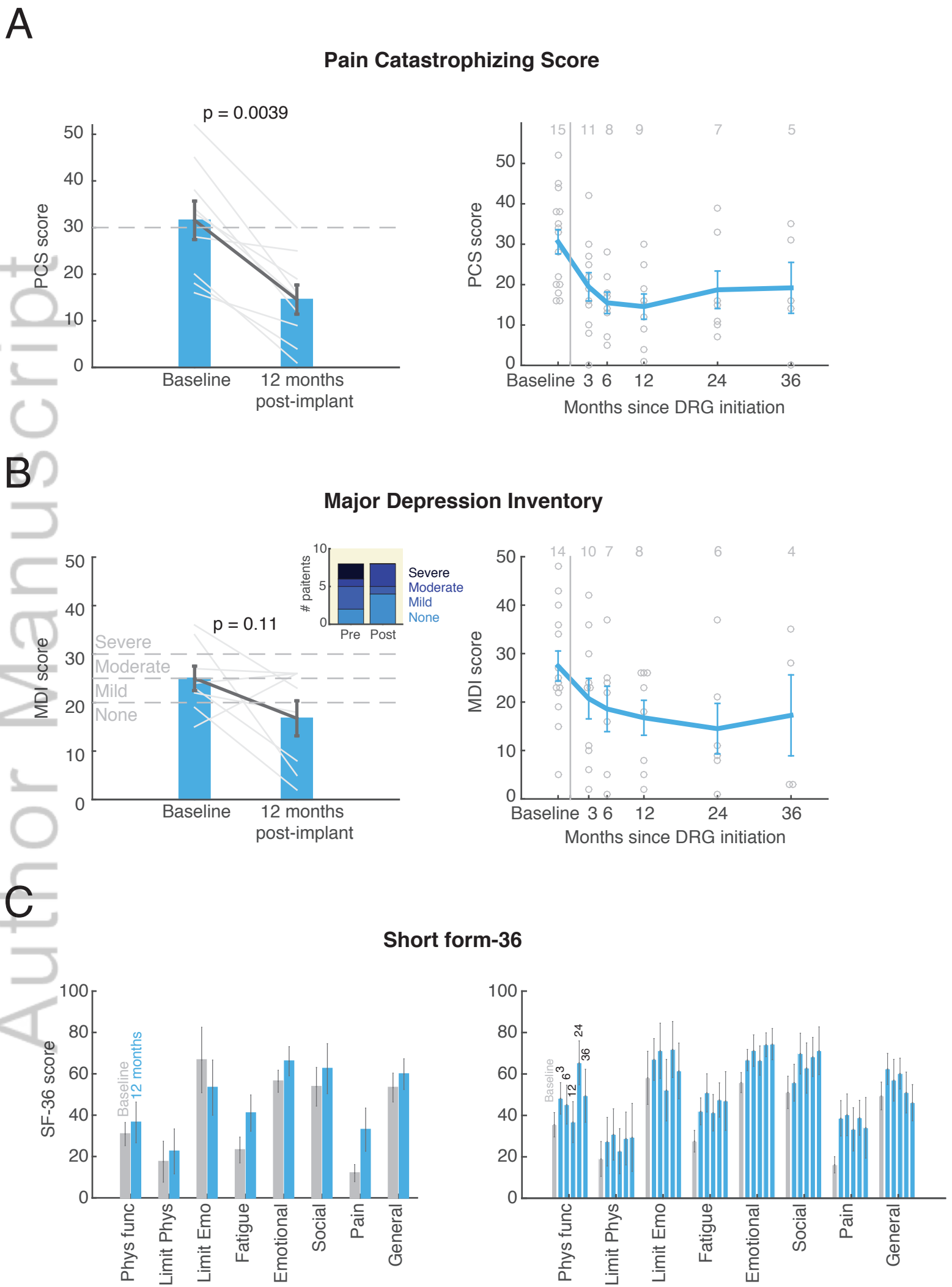

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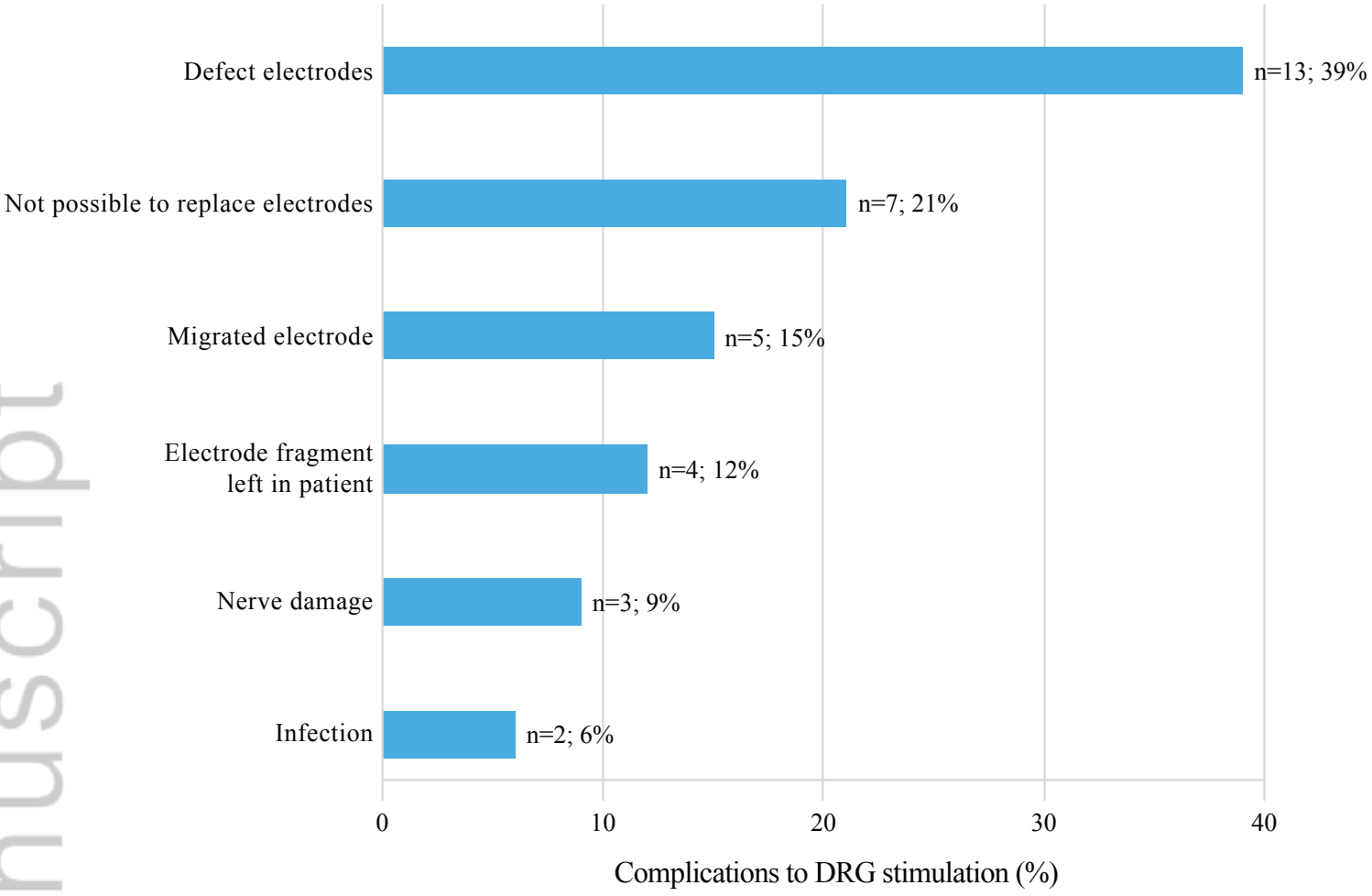

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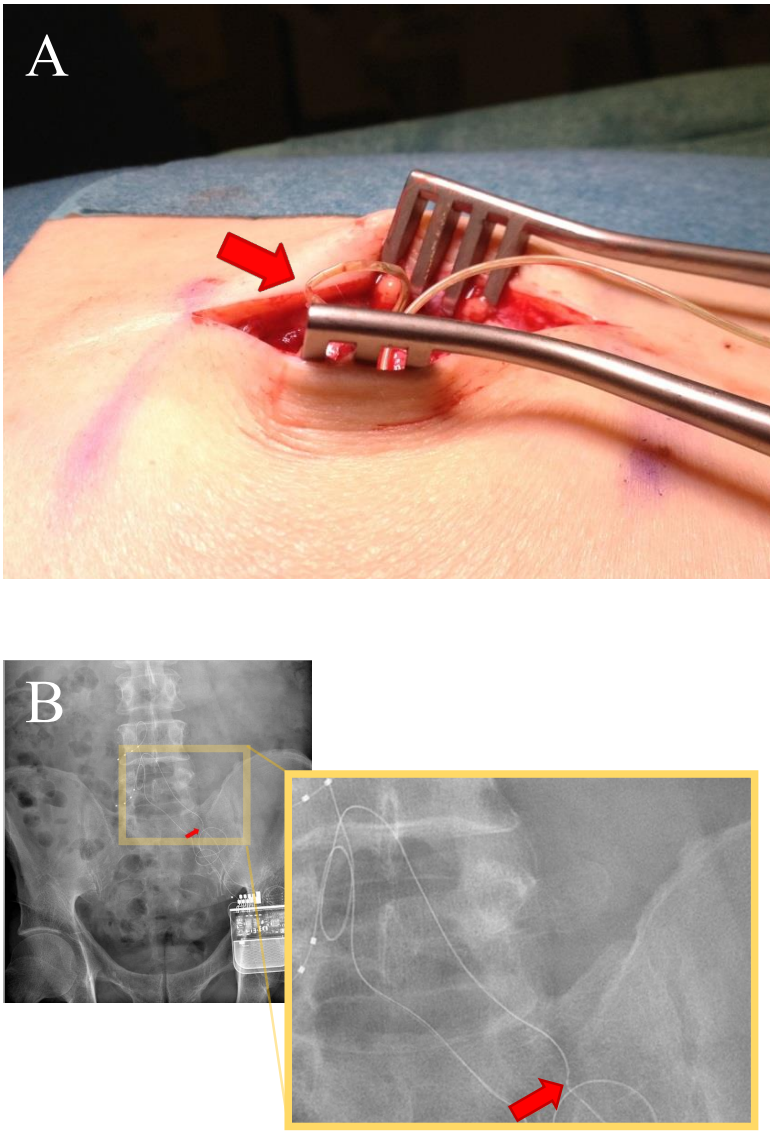

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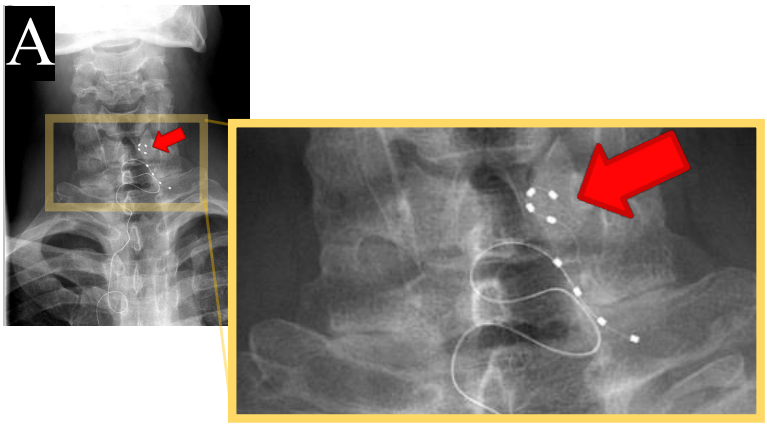

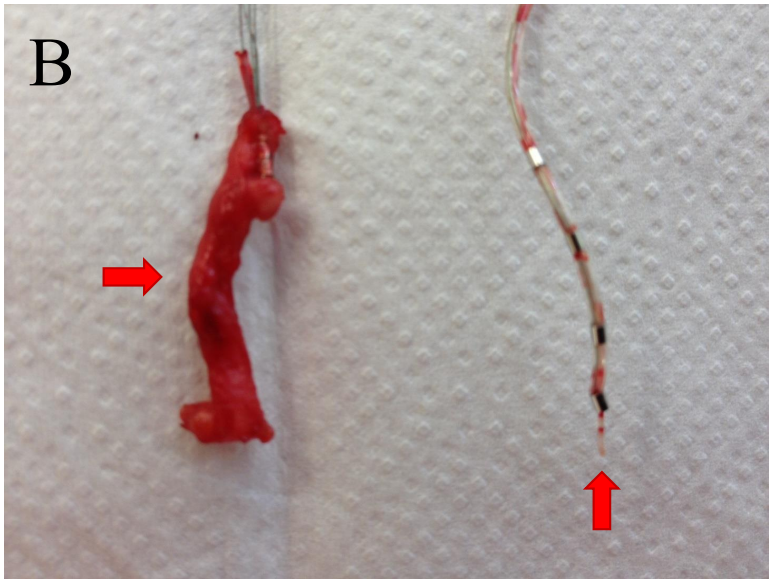

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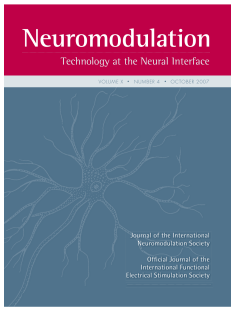

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