The optimal distance between two electrode tips during recording of compound nerve action potentials in the rat median nerve

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Abstract
The distance between the two electrode tips can greatly influence the parameters used for recording compound nerve action potentials. To investigate the optimal parameters for these recordings in the rat median nerve, we dissociated the nerve using different methods and compound nerve action potentials were orthodromically or antidromically recorded with different electrode spacings. Compound nerve action potentials could be consistently recorded using a method in which the middle part of the median nerve was intact, with both ends dissociated from the surrounding fascia and a ground wire inserted into the muscle close to the intact part. When the distance between two stimulating electrode tips was increased, the threshold and supramaximal stimulating intensity of compound nerve action potentials were gradually decreased, but the amplitude was not changed significantly. When the distance between two recording electrode tips was increased, the amplitude was gradually increased, but the threshold and supramaximal stimulating intensity exhibited no significant change. Different distances between recording and stimulating sites did not produce significant effects on the aforementioned parameters. A distance of 5 mm between recording and stimulating electrodes and a distance of 10 mm between recording and stimulating sites were found to be optimal for compound nerve action potential recording in the rat median nerve. In addition, the orthodromic compound action potential, with a biphasic waveform that was more stable and displayed less interference (however also required a higher threshold and higher supramaximal stimulus), was found to be superior to the antidromic compound action potential.

Key Words: nerve regeneration; peripheral nerve injury; compound nerve action potential; median nerve; electrodes; amplitude; supramaximal stimulus intensity; recording electrode; the Project 211 in China; neural regeneration

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Introduction
The compound nerve action potential is evoked from many types of nerve fibers when the nerve trunk is stimulated. The waveform of a compound nerve action potential may include the compound Aαβ wave (such as the motor efferent fiber-Aα; diameter 12–22 μm), touch-pressure sensation afferent fiber-Aβ wave (diameter 5–12 μm), Aδ wave (such as the pain-warm sensation afferent fiber; diameter 1–5 μm), or C wave (such as postganglionic sympathetic fiber; diameter 0.1–1.3 μm)[1-2]. The Aαβ wave of the compound nerve action potential has been studied in the sciatic nerve[3-6], spinal nerve[7-9], tibial nerve[10-12], and peroneal nerve[13-15], as well as in the spinal cord[16-18] and the white matter of the brain[19-21]. The characteristics of Aαβ, Aδ, and C waveforms have been reviewed[22]. The compound nerve action potential, when compared with the traditional electromyogram[23-25], such as compound muscle action potential, possesses the advantages of lower volume conduction, and the ability to be recorded before the regenerated axon extends to the target muscle. The compound nerve action potential is not affected in diseases involving synapses or muscles, and can be measured directly *in vivo*.

The compound nerve action potential has been recorded in many different species, including cats[26-27], rats[5], guinea pig[28-29], monkeys[30] and humans[23]. A similar compound nerve action potential waveform is recorded *in vitro*[31] or *in*

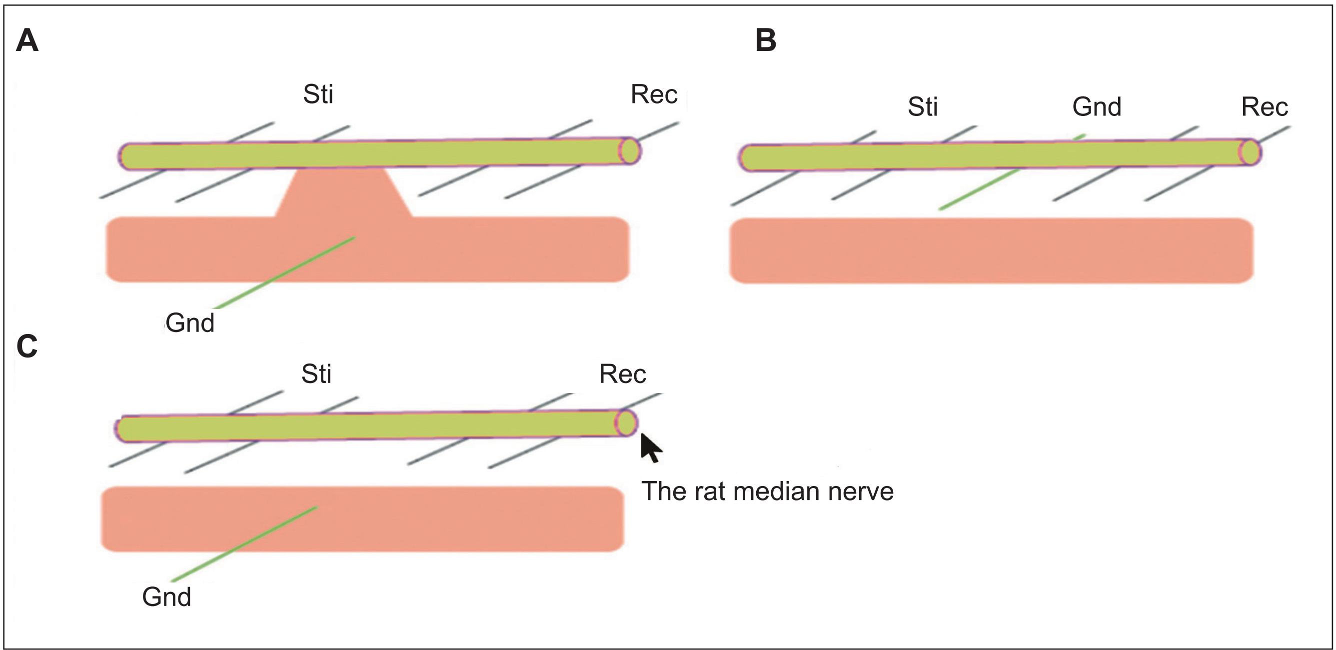

Figure 1 The approaches to compound nerve action potential recording.
Both ends of the median nerve had electrodes placed, leaving the middle part of approximately 4–5 mm intact. The two electrodes were placed under both ends of the nerve trunk, distal and proximal to the middle. The ground wire was inserted into the muscle close to the intact part (Method A; n = 10). In Method B (n = 10), the median nerve was completely dissociated, then otherwise treated as in Method A. In the third approach, the ground wire was placed beneath the middle part of the completely dissociated median nerve trunk (Method C; n = 10). Sti: Stimulating electrodes; Rec: recording electrodes; Gnd: ground wire.

vivo[32]. However, compound nerve action potential amplitudes can present with large disparities, even when they are recorded in the same nerve of the same species[10, 33-34], which might be ascribed to different recording approaches, distances between bipolar electrodes or stimulus strengths. In recent years, there has been a growing focus on upper limb nerve models in studies of peripheral nerves. These possess many advantages, such as fewer contractions and automutilations[35-36], less mobility impairment resulting in the dragging of the affected extremity[37], and less animal distress and care burden. There have been reports incorporating the functional examination of the upper limb nerves[38-40]. To the best of our knowledge, there has been no optimal approach developed to record compound nerve action potentials in the rat median nerve *in vivo*. The compound nerve action potential might fail to be recorded *in vivo*, or its waveform can be significantly affected, due to different distances between the electrodes and different positions of electrodes. Some studies have confirmed that when the distance between the electrodes is 5 mm or more, the amplitude of compound action potentials in frog sciatic nerve *in vitro* is small[41]. Others have reported that the optimal distance between recording electrodes is 3–5 mm for recording compound nerve action potentials in the brachial plexus[42]. But so far, to the best of our knowledge, there has been no study reporting the results when the distance between the electrodes is less than 5 mm. In this study, we used a practical approach and explored the optimal distance between electrodes during recording of compound nerve action potentials in the rat median nerve.

Results

Approaches to compound nerve action potential recording

Both ends of the median nerve, dissociated from the surrounding fascia, had electrodes (about 6–7 mm wide) placed, leaving the middle part of about 4–5 mm intact. The two electrodes were placed under the ends of the nerve trunk, distal and proximal to the middle. The ground wire was inserted into the muscle close to the intact part (Method A). In Method B, the median nerve was completely dissociated, and it was otherwise treated as in Method A. In Method C, the ground wire was placed beneath the middle part of the completely dissociated median nerve trunk. The bipolar electrodes were not allowed to touch the surrounding muscles and fascia tissues, with plastic films used for insulation when necessary (Figure 1).

No compound nerve action potential was elicited by Method B or C. However, compound nerve action potentials could be consistently recorded using Method A with the grounding needle in the neighborhood tissues between the recording and stimulation sites (Figure 2).

Effects of different electrode spacings on compound nerve action potential

When the distances between the stimulating electrodes in the first case were changed from 1.0 to 5.0 mm, the threshold intensity and supramaximal stimulating intensity of the compound nerve action potential were gradually decreased (P < 0.01) and a lower threshold and supramaximal stimulus intensity were needed. Other parameters, such as first-peak amplitude (FPA) and peak-peak amplitude (PPA),

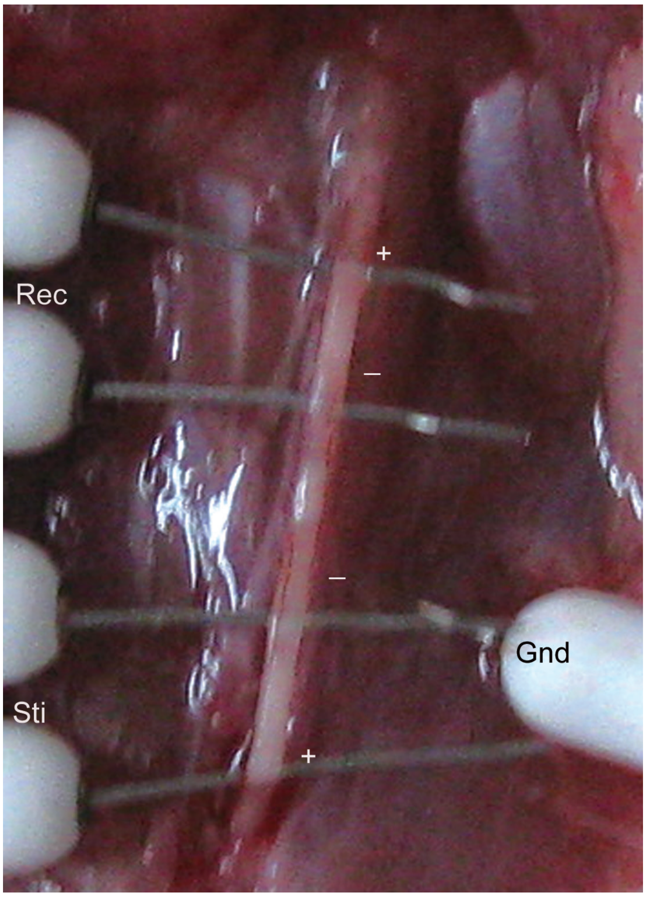

Figure 2 Photograph showing arrangement of recording (Rec) and stimulating (Sti) electrodes and the grounding needle (Gnd).
Two positive electrodes were toward the lateral side, with two negative electrodes toward the medial side, and the electrodes were not allowed to touch the neighboring muscle and fascia tissue around the median nerve.

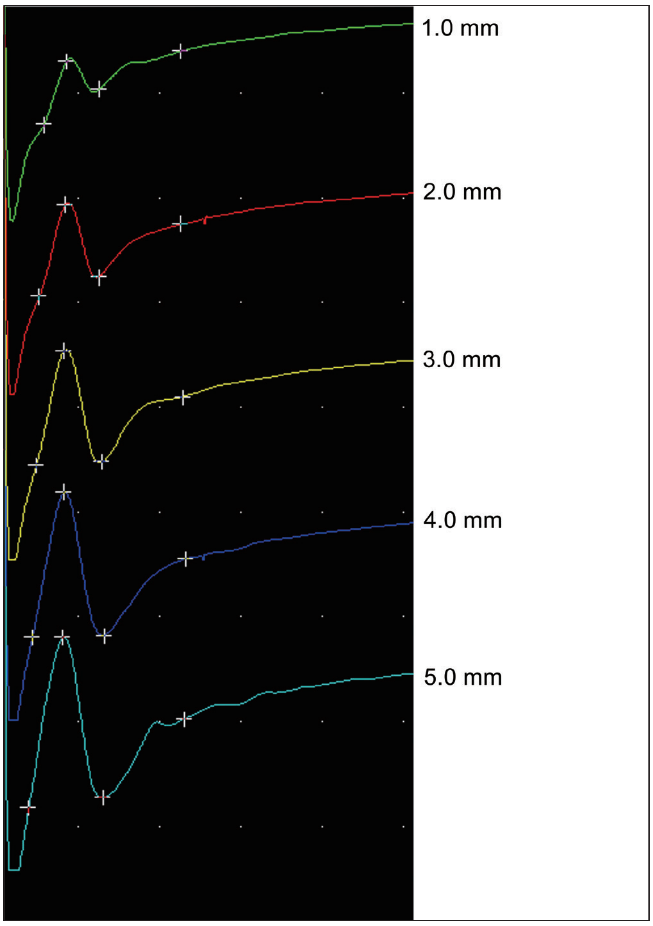

Figure 3 Compound nerve action potential waveform changes with varied distance between two recording needles.
Compound nerve action potential amplitude gradually increases as the distance increases.

latency (LAT) and action potential duration (APD) of the compound nerve action potential were not found to be significantly different between different electrode spacings (P > 0.05; Table 1).

In the second case, the FPA and PPA of compound nerve action potentials were gradually increased when the distance between the recording electrodes changed from 1.0 to 5.0 mm, and higher amplitudes were obtained when a wider distance was used (P < 0.01). Other parameters, such as threshold intensity (THI), SSI, LAT and APD did not show any significant changes (P > 0.05; Table 2, Figure 3).

In the third case, different distances between stimulating electrode and recording electrode (8, 10 or 12 mm) produced no statistically significant effect on compound nerve action potential (P > 0.05; Table 3). In the fourth case, in which the wider spacing of the recording electrodes was the same as that of the stimulating ones, considerably greater FPA and PPA of compound nerve action potentials were observed (P < 0.01) and lower threshold and supramaximal stimulus intensity were needed (P < 0.01). However, LAT and APD of compound nerve action potentials showed no significant differences (Figure 4; P > 0.05).

Comparison of compound nerve action potentials recorded orthodromically or antidromically

The waveform of compound nerve action potentials recorded orthodromically was biphasic, and characterized by more stability and less interference, even though it required a higher threshold of 0.8–3.3 mA and a higher supramaximal stimulus of 1.8–7.8 mA (Figure 5). Antidromically, the waveform was triphasic, and characterized by inconsistency and inaccuracy, despite the lower threshold of 0.1–0.3 mA and lower supramaximal stimulus of 0.9–2.8 mA (Figure 6).

Discussion

Recording of the compound muscle action potential, a classic electrophysiological method, has diagnostic and prognostic value for assessing peripheral nerve injury[43]. But it cannot be recorded until the regenerated nerve extends to the target muscle, and the compound muscle action potential is influenced by volume conduction and synaptic function. However, compound nerve action potential recording is a useful tool in the surgical management of many kinds of peripheral nerve diseases, including nerve injuries[44], neuropathy[45], and neuroma[46-47]. The presence of a compound

Table 1 Effect of different distances between stimulating electrode needles on compound nerve action potential

Variable	1.0 mm	2.0 mm	3.0 mm	4.0 mm	5.0 mm	*F*	*P*
FPA (mV)	5.17±2.45	6.00±2.27	6.15±1.92	6.82±1.92	6.69±1.74	2.001	0.101
PPA (mV)	6.06±3.46[a]	7.19±3.11[a]	7.22±2.81[a]	8.86±2.40[a]	9.49±2.23[a]	4.780	0.001
THI (mA)	7.83±2.95[a]	5.03±1.78[a]	3.56±1.43[a]	2.64±1.03[a]	2.12±0.74[a]	33.840	0.000
SSI (mA)	14.36±5.57[a]	11.48±4.71[a]	8.55±4.23[a]	7.51±3.86[a]	5.60±2.68[a]	10.434	0.000
LAT (ms)	0.86±0.12	0.85±0.10	0.86±0.12	0.86±0.09	0.85±0.09	0.189	0.944
APD (ms)	3.10±0.17	3.07±0.18	3.07±0.19	3.16±0.22	3.10±0.19	0.767	0.549

Data are presented as mean ± SEM, and one-way analysis of variance followed by Student-Newman-Keuls test was applied to comparisons between different electrode spacing groups. There were significant differences in PPA, THI and SSI of compound nerve action potentials recorded orthodromically between different electrode needle spacings ($P < 0.01$). However, no significant differences were found in FPA, LAT or APD between different electrode spacing groups ($P > 0.01$). FPA: First-peak amplitude; PPA: peak-to-peak amplitude; THI: threshold intensity; SSI: supramaximal stimulating intensity; LAT: latency; APD: action potential duration. Superscript "a" indicates that there are significant differences between different electrode spacing groups ($P < 0.01$).

Table 2 Effects of different distances between recording electrode needles on compound nerve action potential

Variable	1.0 mm	2.0 mm	3.0 mm	4.0 mm	5.0 mm	*F*	*P*
FPA (mV)	1.54±0.99[a]	2.64±1.16[a]	3.93±1.32[a]	5.25±1.67[a]	7.07±1.74[a]	47.681	0.000
PPA (mV)	2.24±1.45[a]	3.56±1.67[a]	5.41±1.91[a]	6.99±2.29[a]	9.19±2.42[a]	38.409	0.000
THI (mA)	3.33±2.64	2.62±1.03	2.32±1.05	2.30±0.87	2.24±0.72	1.926	0.112
SSI (mA)	8.44±6.76	7.45±4.52	6.76±4.48	6.96±4.10	5.39±2.53	1.128	0.348
LAT(ms)	0.87±0.10	0.83±0.09	0.84±0.10	0.85±0.10	0.85±0.10	0.497	0.738
APD (ms)	3.08±0.21	3.10±0.18	3.07±0.18	3.11±0.16	3.06±0.18	0.270	0.897

Data are presented as mean ± SEM, and one-way analysis of variance followed by Student-Newman-Keuls test was applied to comparisons between different electrode spacing groups. There were significant differences in FPA and PPA of compound nerve action potentials between different electrode needle spacings ($P < 0.01$). No significant differences were found in THI, SSI, LAT or APD between different electrode needle spacings ($P > 0.05$). FPA: First-peak amplitude; PPA: peak-to-peak amplitude; THI: threshold intensity; SSI: supramaximal stimulating intensity; LAT: latency; APD: action potential duration. Superscript "a" indicates that there are significant differences between different electrode spacing groups ($P < 0.01$).

Table 3 Effects of different distances between stimulating electrodes and recording electrodes on compound nerve action potential

Variable	8 mm	10 mm	12 mm	*F*	*P*
FPA (mV)	6.25±2.06	6.57±1.85	6.65±2.02	0.227	0.792
PPA (mV)	8.71±2.53	9.08±2.28	8.90±2.50	0.119	0.888
THI (mA)	2.20±0.83	2.33±0.72	2.33±0.79	0.181	0.835
SSI (mA)	6.46±5.00	5.76±2.80	6.83±4.98	0.310	0.735
LAT (ms)	0.86±0.08	0.85±0.10	0.89±0.10	1.119	0.334
APD (ms)	3.08±0.18	3.07±0.18	3.03±0.20	0.505	0.606

Data are presented as mean ± SEM, and one-way analysis of variance followed by Student-Newman-Keuls test was applied to the comparisons between different groups. Different distances between stimulating electrodes and recording electrodes produced no significant effect on compound nerve action potential parameters ($P > 0.05$).

nerve action potential is associated with a 90% recovery to a useful motor state. Therefore, compound nerve action potential recording can provide useful information regarding the regenerative potential of a damaged nerve long before that potential is clinically evident[42].

Compound nerve action potential is the total electrical potential that develops and travels within a nerve. Once a stimulus exceeds the fiber thresholds of a nerve, a maximal potential will be generated that will represent the electrical summation of different types of nerve fiber potentials[4]. But differences in the recorded compound nerve action potential amplitude can be significant, even in the same nerve, *e.g.*, the sciatic nerve[48]. Therefore, designing and developing a standard and optimal compound nerve action potential recording approach would be valuable for experimental research and clinical diagnosis.

In the current study, compound nerve action potentials failed to be elicited when the rat median nerve was completely dissociated from the surrounding fascia, regardless of the ground wire position. It was previously reported that compound nerve action potentials were recorded in the rat sciatic nerve when the tibial nerve was stimulated[34], which suggested that compound nerve action potentials could be elicited if both ends of the dissociated median nerve had electrodes placed, leaving the middle part of about 4–5 mm intact. In so doing, compound nerve action potentials were found to be elicited every time, with amplitudes close to those recorded in sciatic nerve *in vitro*[31]. Therefore, we believe that this approach could be of significant value, because a compound nerve action potential was elicited at the dis-

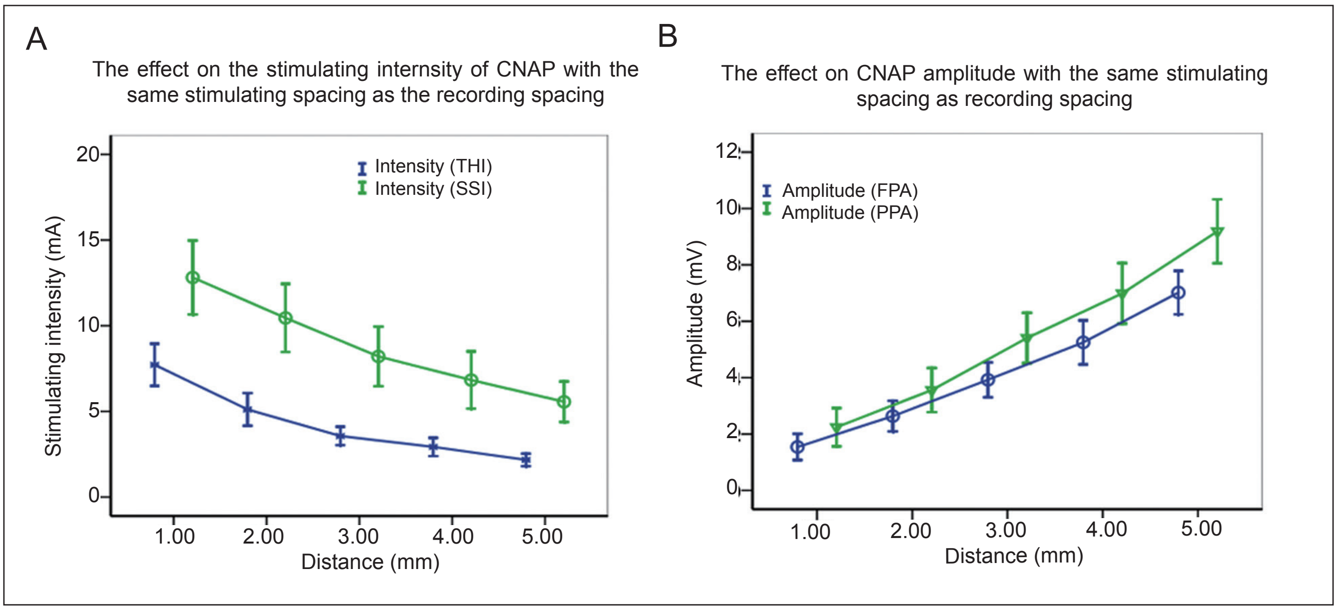

Figure 4 Changes in compound nerve action potential (CNAP) parameters when different stimulating spacings (the same as the recording spacings) were used for recording CNAP.
THI and SSI (A) of compound nerve action potentials individually were significantly different between different distances ($P < 0.01$). FPA and PPA (B) of compound nerve action potentials individually were significantly different between different distances ($P < 0.01$). THI: Threshold intensity; SSI: supramaximal stimulating intensity; FPA: first-peak amplitude; PPA: peak-to-peak amplitude.

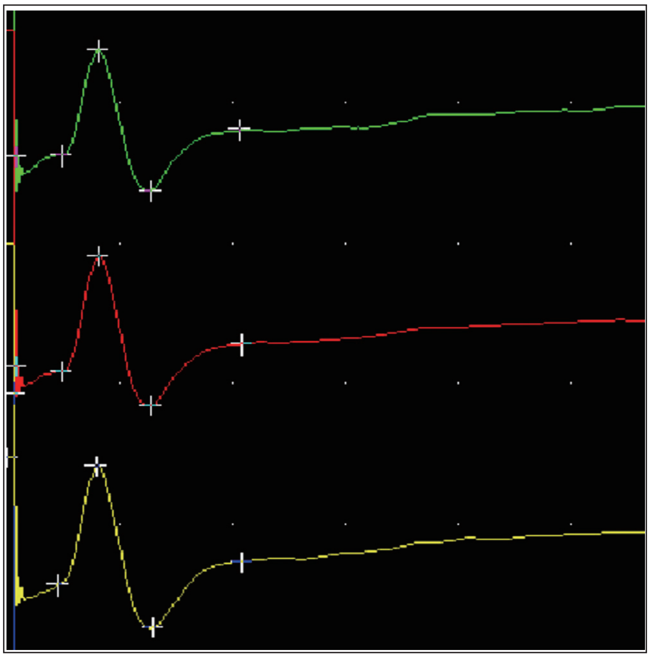

Figure 5 Changes in compound nerve action potential waveform recorded orthodromically in the rat median nerve.
The waveform was biphasic, and characterized by more stability and less interference, even though it required a higher threshold of 0.8–3.3 mA and a higher supramaximal stimulus of 1.8–7.8 mA. Different colored waveforms represent different channels of the waveform recorded.

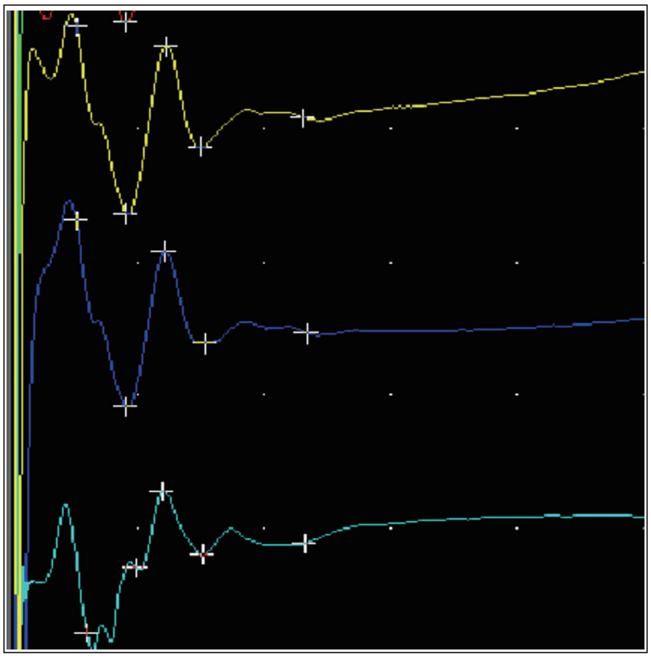

Figure 6 Changes in compound nerve action potential waveform recorded antidromically in the rat median nerve.
The waveform was triphasic, and characterized by inconsistency and inaccuracy, despite the lower threshold of 0.1–0.3 mA and lower supramaximal stimulus of 0.9–2.8 mA. Different colored waveforms represent different channels of the waveform recorded.

tance of 8 mm between the stimulating and recording sites. Clinically, compound nerve action potentials are only elicited at a distance of over 4 cm between the corresponding sites in the human peripheral nerve. This difference could be ascribed to the smaller diameters of the rat median nerve and electrode needles. Our results showed that compound nerve action potentials recorded orthodromically required both a higher stimulating threshold and supramaximal intensity, but produced a consistent biphasic wave. Antidromically, the waveform of compound nerve action potentials consisted of a triphasic wave, which was unstable and significantly deviated from the baseline. The biphasic wave was found to be similar to compound nerve action potentials reported previously[49]. The compound nerve action potential could be stably recorded only if the electrodes were placed appropriately, with the middle part of the median nerve (about 4–5 mm) intact.

Our results further showed that compound nerve action potential amplitude increased, while the threshold and supramaximal stimulus intensity decreased gradually when the distances between the recording or stimulating electrodes were increased from 1.0 to 5.0 mm. In male bullfrog isolated sciatic nerve, Dalkilic et al.[50] found that when the recording electrode spacing changed (from 10 mm up to 55 mm the compound nerve action potential amplitude decreased gradually, duration and latency increased gradually, but the area under the waveform had no significant change. The amplitude in the aforementioned study was 5–8 mV, with action potential duration 2.5–3.5 ms and latency 0.7–2 ms. Other studies showed that as the distance between the electrodes increases (from 0.5 to 1.0, 1.5, 2.0 or 2.5 cm), the volatility becomes gradually smaller, with the waveform relatively close to the standard two-way wave between the recording electrode, and conversely, that the volatility increased as the distance between the electrodes decreased, with more complex waveforms, of multiphase wave or gravity waves and broadening stimulus artifact increases[22]. Tiel et al.[42] argued that the separation between the bipolar tips of the electrodes on the recording end of 3 to 5 mm worked well in general, and that if the distance was too short, the potential difference detected would be reduced, because both electrodes were placed in the active region of the nerve. In our study, there was a gradual increase in compound nerve action potential amplitude when the distance between the recording electrodes was scaled up from 1.0 to 5.0 mm, suggesting that the distance of 5 mm between the recording or stimulating electrodes is optimal for compound nerve action potential recording in the rat median nerve. Furthermore, compound nerve action potential recording showed no statistically significant differences when the distances between the recording and stimulating sites was changed from 8 to 12 mm. In line with previous studies[50-51], the range of compound nerve action potential amplitudes in the median nerve was from 5 to 13 mV. In the 20 right median nerve, the length of the median nerve trunk at the upper arm was about 18–22 mm, and the maximal distance between the recording electrodes or between the stimulating electrodes was about 5.0 mm. A limitation of our experiments was that no longer nerve was available, hence we were unable to test distances greater than 5 mm. Therefore, the distance of 5 mm between the recording and stimulating electrodes is optimal for compound nerve action potential recording in the rat median nerve.

In summary, compound nerve action potentials were recorded orthodromically by Method A in the median nerve, with the same distance (5.0 mm) between the two stimulating needles as that between the two recording needles, and a distance of 10 mm between recording and stimulating sites. Other parameters were 2.5 ms scan speed, 5 mV wave amplitude per division, 0.1 ms duration square wave for stimulation, 1Hz stimulating frequency, and 10 to 1,000 Hz filtration.

The method and optimal parameters revealed in the current study could be used in related research fields (such as brachial plexus injury, peripheral nerve damage, optic nerve damage and auditory nerve damage). In particular, these results provide a valuable reference for the clinical diagnosis and assessment of short injured nerves, using the compound nerve action potential recording technique together with compound muscle action potential.

Materials and methods

Design

Matched pairs design.

Time and setting

The experiments were performed at Experimental Animal Center of Fudan University in China in June 2011.

Materials

Twenty Sprague-Dawley male rats (10 weeks old, 280–330 g), were purchased from Experimental Animal Center of Fudan University in China (license No. SYXK (Hu) 2009-0082). Ethically, the experiments were approved by Fudan University Animal Care and Use Committee in China. All efforts were made to minimize the number of animals used and their distress.

Methods

Median nerve preparation

Each rat was anesthetized by intraperitoneal injection of 1% sodium pentobarbital solution (40 mg/kg), and placed in the dorsal position.

A longitudinal incision was performed at the anteromedial site extending from the ectopectoralis to the elbow region, with the right median nerve exposed over the length of the upper arm. The nerve was continuously moistened with normal saline to avoid desiccation.

Electrophysiological measurement

Compound nerve action potentials were recorded with 0.2 mm diameter bipolar stainless steel electrodes (Medtronic Keypoint Systems, Dantec corporation, Denmark). Recording parameters were scan speed 2.5 ms, wave amplitude 5 mV per division, stimulus square wave duration 0.1 ms, stimulating frequency 1 Hz, and filtration from 10 to 1,000 Hz. Distances were measured with a vernier caliper, and skin temperature was maintained at approximately 36°C (Vital Sense Monitor, American Health & Medical Supply International Corp) in a room maintained at a constant temperature of 26°C. Three different methods (Method A, B and C; Figure 1) were used to record compound nerve action potentials. The bipolar electrodes were not allowed to touch the surrounding muscles and fascia tissues, with plastic films used for insulation when necessary.

To explore optimal electrode distances, compound nerve action potentials were recorded with various distances between electrodes. In the first case, compound nerve action potentials were elicited with distances of 1.0, 2.0, 3.0, 4.0 or 5.0 mm between the two needles of the stimulating electrode, while the distance between the two needles of the recording electrode was maintained at 5.0 mm. Conversely, in the second case, five different distances between the two needles of the recording electrode were tested, while the distance between the two needles of the stimulating electrode was kept at 5.0 mm. In the third case, distances of 8, 10 and 12 mm between the recording and stimulating sites were tested, while the distances between the recording and stimulating electrode needles were kept constant. In the fourth case, wider spacing of the recording electrodes (the same as that of the stimulating electrodes) was applied and the effects on compound nerve action potential were analyzed. Finally, the parameters of compound nerve action potentials recorded orthodromically (recorded in the proximal segment with the distal segment stimulated), were compared with those recorded antidromically, in terms of waveform, baseline and amplitude.

Statistical analysis

The data were analyzed using the SPSS 16.0 software package (IBM Corporation, New York, NY, USA) and are presented as mean ± SEM. One-way analysis of variance followed by Student-Newman-Keuls test was applied for comparisons of amplitude, stimulating intensity, latency and action potential duration between different groups. A value of $P < 0.05$ was considered statistically significant.

Author contributions: *Li YP was responsible for animal preparation, data acquisition and integration, analyzed experimental data, drafted the paper and provided data support. Lao J had full access to study concept and design, validated the paper and was in charge of funds. Zhao X participated in statistical analysis. Tian D was responsible for electrophysiological testing. Zhu Y was responsible for electrophysiological method design and electrophysiological testing. Wei XC participated in study design and statistical analysis. All authors approved the final version of this paper.*

Conflicts of interest: *None declared.*

Peer review: *This study found the optimal distance, including the distance between two recording electrode tips, the distance between two stimulating electrode tips and the distances between recording and stimulating sites, when compound nerve action potential was recorded in rat median nerve. These findings provide some help in the evaluation and treatment of short injured nerve using compound nerve action potential in the clinic.*

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