

**Reliability of sympathetic skin response in individuals with spinal cord injury:
a supraorbital nerve stimulation approach**

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Abstract

Objectives: To assess the test-retest reliability of sympathetic skin response (SSR) using supraorbital nerve stimulation method in individuals with spinal cord injury (SCI).

Study design: Psychometric property testing.

Setting: A rehabilitation facility in Chiang Mai, Thailand.

Methods: SSR was done on two executive days in individuals with SCI, stimulating at supraorbital nerve and recording at the palmar and plantar surface of both hands and feet.

Results were reported as hand- and foot-SSR scores. Test-retest reliability was analyzed using intraclass correlation coefficients (ICC).

Results: Forty individuals with SCI were recruited. ICC of hand and foot SSR scores were 0.963 (95%CI: 0.888-0.967) and 0.833 (95%CI: 0.707-0.908), indicating excellent and good test-retest reliability, respectively. Subgroup analyses showed a problematic decrease in test-retest reliability to a moderate level of the foot SSR score in the elderly subgroup (age \geq 60).

Conclusion: SSR induced by the supraorbital nerve stimulation showed excellent test-retest reliability for hand SSR and good reliability for foot SSR in the overall SCI population. SSR, induced by supraorbital nerve stimulation method and reported by SSR score, should be a reliable tool for evaluating autonomic functions in individuals with SCI.

Keywords: Spinal Cord injuries, Reliability, Test-retest, Sympathetic nervous system,
Autonomic nervous system

Introduction

Spinal cord injury (SCI) is a serious neurological condition that often results in permanent motor and sensory impairments. It can lead to various complications, including infections, and pressure injuries. These issues contribute to a significantly increased burden on affected individuals. In 2019, the global incidence of SCI was approximately 0.9 million cases, with a prevalence of 20.6 million cases [1, 2]. In addition to motor and sensory impairments, an autonomic nervous system is disturbed after SCI, resulting in autonomic dysfunction [3, 4]. For instance, autonomic dysreflexia (AD) and orthostatic hypotension (OH) are common after SCI as it is prevalent in 74% of individuals with SCI [5]. These autonomic dysfunction syndromes could postpone the post-acute rehabilitation program, resulting in a delayed achievement of optimal functions of the individuals. A result from the previous study demonstrated that 59% of individuals with SCI who experienced OH would have relevant symptoms that prevent therapy sessions during their in-patient rehabilitation [6]. Therefore, an evaluation method aiming to early detect autonomic dysfunction, causing a timely intervention, is necessary for successfully obtaining the optimized functions of individuals with SCI as soon as possible.

However, symptoms of autonomic dysfunction, such as recurrent syncope, dizziness, headache, or coat-hanger pain for OH [6] and headache, flushing, and sweating for AD [7], are non-specific, and the mechanisms underlying those symptoms have not been completely understood, but tend to be multifactorial [8], leading to diagnostic difficulty. Therefore, an investigation aiming to assess autonomic functions might have a crucial role in accurately identifying the causes of these non-specific multifactorial symptoms. Sympathetic skin

response (SSR) is an electrodiagnostic study aiming to evaluate abnormalities in the autonomic nervous system pathway. It has been widely used because it is convenient, easy, and non-invasive. SSR assesses an afferent sensory pathway, with the involvement of non-myelinated C-fibers as well as myelinated A-delta and A-beta fibers, depending on the mode of stimulation, and efferent sympathetic cholinergic pathway, which are related to the control of sweating [9]. Despite no standard consensus for reporting, results of SSR could be reported in either a qualitative fashion by assessing whether it elicited or not or quantitative fashion by evaluating its amplitude and latency. However, since the amplitude and latency SSR is sensitive to many contributing factors, including emotion and habituation of the examinee [10], room and skin temperature [11, 12], age [13], and intensity or method of stimulation [14], many literatures reported that a qualitative assessment, i.e., the SSR score, is more preferred [14]. In brief, SSR is recorded as a compound electrodermal signal resulting from postganglionic sympathetic activity influencing sweat gland function at the skin of the hands and feet, following a sympathetic stimulus such as electrical stimulation at the median, tibial, or supraorbital nerve [14].

In individuals with SCI, a previous study demonstrated that SSR induced by median nerve stimulation and deep breath maneuver had high test-retest reliability [9]. However, there were some limitations regarding the method and the interpretation of SSR in the previous study. First, individuals with SCI, especially those with tetraplegia have abnormal sensations in their upper extremities, causing a risk of obtaining inadequate sympathetic stimulation when using a median nerve stimulation method. Therefore, a supraorbital nerve stimulation might be more suitable in individuals with SCI since it is not involved in the

injury. Second, the previous study did not control skin temperature, which could influence the results of SSR, as well as did not mention blinding the clinical information of the participant to the interpreter, which could be a risk of assessment bias [9]. These limitations lead to the objective of this study, which is to evaluate the test-retest reliability of SSR study in individuals with SCI, using the supraorbital stimulation method and SSR score, as well as controlling skin temperature and blinding the interpreter. We aim to improve diagnostic accuracy to support timely interventions and better rehabilitation outcomes for individuals with SCI-related autonomic dysfunction.

Methods

This psychometric property testing study was approved by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (Study code REH-2564/08268). It was conducted in the rehabilitation ward of Maharaj Nakorn Chiang Mai Hospital, which is an SCI-specialized rehabilitation facility in Thailand.

Participants

Individuals at the age between 18-80 years old, currently in a post-acute (more than one month) to chronic (equal to or more than one year) phase after SCI, were recruited from the rehabilitation ward of Maharaj Nakorn Chiang Mai Hospital between September 2021 to January 2023. Individuals with diabetic mellitus, history of facial trauma, unstable medical condition, vital signs, or uncooperative during the examination were excluded from the study. Before conducting the SSR protocol, a nerve conduction study of bilateral median nerves and bilateral medial plantar cutaneous nerves would be investigated and individuals with

bilaterally absent sensory nerve action potential (SNAP) of median nerve or compound nerve action potential (CNAP) of medial plantar cutaneous nerve would also be excluded.

Sample size

The sample size was calculated using a formula for estimating correlation as follows,

$$N = [(Z_{\alpha} + Z_{\beta}) / C]^2 + 3$$

$$C = 0.5 * \ln[(1+r)/(1-r)]$$

Z_{α} = standard deviation for α (1.96)

Z_{β} = standard deviation for β (1.28)

r = estimation of the expected correlation coefficient from the pilot study, previous or referred study

The sample size was calculated using an r -value of 0.735 from the previous study [9], resulting in 15 participants for hand SSR. A pilot study with 5 patients with SCI assessed the foot SSR score, yielding an ICC of 0.5 and a calculated sample size of 38. To account for potential exclusions due to technical issues, the final sample size was set at 40.

Equipment

The Dantec Keypoint (Medtronic) workstation, version 22022, originating from Denmark, was utilized as electrodiagnostic equipment to evaluate SSR. Skin temperature was measured using the Yuwell YT-1 infrared thermometer from China.

Study protocol

After obtaining signed informed consent, median nerve, and medial plantar cutaneous nerve conduction studies were performed bilaterally in all participants. The participants were excluded in this step if the SNAP/CNAP of any of those nerves were absent. Then, an SSR study was performed by one investigator (TB). First, the skin on both hands and feet was cleaned to reduce electrical impedance. After that, the temperature on both hands and feet was measured. The skin would be warmed to keep the temperature higher than 32 °C (89 °F). Then, electrodes were placed in bilateral palms and soles. Electrical stimulations were done at the supraorbital nerve five times with an intensity of 30 mA and a duration of 0.2 msec, using unilateral site stimulation. The cathode is placed at the supraorbital notch above the inner edge of the eyebrow, and the anode is placed on the forehead about 2.5 centimeters away from the cathode. The interval between each stimulation was 60 seconds to decrease habituation. Peak-to-peak amplitude was obtained separately from both hands and feet. The setting of the SSR protocol used in this study is illustrated in **Figure 1**. The score was counted as one if the amplitude was more than 0.05 mV and counted as zero if the amplitude was less than 0.05 mV. The raw SSR result was assessed and interpreted by an interpreter (ST) who was blinded to the clinical information of the participant to decrease assessment bias. Raw SSR scores of both hands (maximum of each side = 5, total score = 10) were summated and reported as a hand SSR score. Raw SSR scores of both feet were also summated and reported as a feet SSR score. This method was repeated on the next executive day by the same investigator (TB) and interpreter (ST).

Statistical analysis

All statistical analysis was performed using SPSS software version 26.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp.). A p-value less than 0.05 was considered statistically significant. Characteristics and SSR scores of the participants were described using n (%) for categorical variable and mean (SD) or median (25th, 75th percentile) according to their distribution, for continuous variable.

Test-retest reliability was analyzed using intraclass correlation coefficients (ICC). Since an assumption for using ICC is homoscedasticity, which means both sets of data would have similar variance, differences of the variance of both hands and foot SSR scores from the first and the second assessment were analyzed using analysis of variance (ANOVA) [15]. If homoscedasticity had been assumed, ICC would have been performed using a two-way mixed effects model with an absolute degree definition. Subgroup analyses of ICC were performed to determine the test-retest reliability of SSR score in specific subgroup of individuals with SCI according to age (age < or ≥ 60 years old), obesity using SCI-specific body mass index (BMI) cut-off point (BMI ≤ or > 22.0 kg/m²) [16], etiology (traumatic or non-traumatic), level (tetraplegia or paraplegia), completeness (complete or incomplete), and duration of SCI (post-acute or chronic). ICC would be interpreted as ‘poor’ (0.00–0.50), ‘moderate’ (0.51–0.75), ‘good’ (0.76–0.90), or ‘excellent’ (0.91–1.00) [15].

Results

Of 43 individuals who were initially screened, 1 individual (2.3 %) was excluded due to absent median SNAP, 1 individual (2.3 %) was excluded due to being concomitantly diagnosed with motor neuron disorder, and 1 individual (2.3 %) was excluded due to

unwilling to participate. Therefore, 40 individuals (93.0%) with SCI were included in this study. Most participants were male (29, 72.5%). The mean (SD) age was 43 (15) years old. Twenty-five (62.5%) participants were in the post-acute phase of SCI and 15 participants (37.5%) were in the chronic phase of SCI. The major cause of SCI was trauma-related (32, 80%). Most of the participants were diagnosed with AIS A, i.e., complete injury (19, 47.5 %). Most of the participants had cervical SCI, resulting in tetraplegia (18, 42.5%). According to the SCI-specific cut-off level of BMI for diagnosing obesity, 17 participants (42.5%) were obese. Characteristics of the participants were presented in **Table 1**.

SSR scores of the participants were presented in **Table 2**. The mean (SD) hand SSR scores of the first and the second assessment were 2.74 (2.24) and 2.75 (2.26), respectively. The mean (SD) foot SSR scores of the first and the second assessment were 1.14 (1.91) and 0.96 (1.84), respectively. Noteworthy, the hand SSR score of 11 participants (27.5%) and the foot SSR score of 26 participants (65%) were zero, indicating that there was no SSR detected in those individuals.

The test-retest reliability of SSR score for overall participants and participants in each subgroup were presented in **Table 3**. The ICC of hand and foot SSR scores were 0.963 and 0.833, indicating excellent and good test-retest reliability, respectively. Focusing on the subgroup analyses of test-retest reliability of hand SSR score, the ICC of hand SSR score in all subgroups was between 0.911-0.974, indicating excellent test-retest reliability. The ICC of foot SSR score was 0.825 for participants who were not obese and 0.848 for those who were obese, 0.810 for participants who had traumatic SCI and 0.995 for those who had non-traumatic SCI, 0.801 for participants who had complete SCI, and 0.844 for those who had

incomplete SCI, and 0.817 for participants who were in post-acute phase of SCI and 0.876 for those who were in the chronic phase of SCI. These results indicate that the test-retest reliability of foot SSR score was good to excellent regardless of the obesity status, etiology, completeness, and duration of SCI. On the other hand, the ICC of foot SSR score of participants whose ages were less than 60 years old was 0.886, indicating good test-retest reliability whereas the ICC of foot SSR of those whose ages were 60 years old or more was 0.540, indicating moderate test-retest reliability. Also, the ICC of foot SSR score of participants who had paraplegia was 0.864, indicating good reliability whereas the ICC of foot SSR score of participants who had tetraplegia was 0.756, indicating moderate to good test-retest reliability. Therefore, there was a slight decrease in the test-retest reliability of the foot SSR score in the tetraplegia subgroup but a problematic decrease in the test-retest reliability of the foot SSR score in the elderly subgroup.

Discussion

This study found that, in individuals with SCI, SSR induced by supraorbital nerve stimulation and reported by the hand and foot SSR scores had excellent and good test-retest reliability, respectively. However, it was also demonstrated that the SSR foot score in our study had less reliability than the hand SSR score (ICC of 0.833 vs ICC of 0.963, respectively). This difference might be due to the differences in characteristics of SSR in the individuals with SCI participating in this study. The hand SSR was expected to be similarly normal in all participants with paraplegia, regardless of completeness, causing a ceiling effect that potentially increased test-retest reliability. On the other hand, the foot SSR could vary, depending on the completeness, both in participants with tetraplegia and paraplegia, causing

lesser ceiling effect and lower test-retest reliability. In addition, since SSR is influenced by emotion [10] and age [13], the foot SSR, which had a smaller amplitude than the hand SSR [9], is more susceptible to being influenced, causing misinterpretation of the foot SSR from present with very small amplitude to absent.

A previous study also demonstrated excellent reliability of SSR induced by median nerve stimulation [9]. However, the test-retest reliability of foot SSR in our study was lower than those in the previous study (ICC of 0.833 vs ICC 0.958, respectively [9]). This inconsistency might be due to the differences in characteristics of SSR between our study and the previous one. The mean foot SSR in the previous study [9] was lower than those in our study and 72% of the participants in the previous study had absent foot SSR (score 0), causing a floor effect which potentially increased test-retest reliability. This might be a potential explanation of whether the test-retest reliability of foot SSR was higher in the previous study when compared with our study. In addition to SCI, the reliability of SSR has also been demonstrated in other autonomic-related conditions. The previous study in individuals with primary palmar hyperhidrosis showed good to excellent intra-rater reliability of SSR amplitude and latency [17], supporting its consistency across different clinical populations. In subgroup analyses, the hand SSR demonstrated excellent test-retest reliability in all subgroups, indicating that hand SSR could be reliably used in individuals with SCI regardless of their demographic and SCI characteristics. On the other hand, there was a problematic decrease (from excellent to moderate, ICC=0.540) in the test-retest reliability of the foot SSR score in the elderly subgroup. This inconsistency might be due to the low sample size of this subgroup (n=6), causing a wide, across zero 95%CI (-0.160 to 0.913), which indicates a poor

precision of an ICC value. Focusing on the possible mechanism, the study found that older participants tended to have lower amplitudes of SSR than younger participants [13]. Therefore, similar to the explanation of the lower test-retest reliability of the foot SSR previously discussed, smaller amplitudes of SSR found in the elderly might be susceptible to misinterpretation to be absent, causing lower test-retest reliability in the elderly subgroup. Relatively low test-retest reliability was also demonstrated in tetraplegia subgroups. This might also be due to the instability in the autonomic spinal pathway (in participants with tetraplegia, especially those with incomplete lesions) between the first and the second assessment date. Such variability is supported by previous studies, which have demonstrated that in individuals with incomplete SCI, the presence and characteristics of SSR may fluctuate considerably. This could account for the observed inconsistencies in test-retest reliability [18]. However, despite having lower ICC when compared with those of other subgroups, the ICC of foot SSR score in the tetraplegia subgroup still falls at a moderate to good level, indicating acceptable test-retest reliability in these subgroups. Finally, although a previous report showed reappearance of SSR below the lesion during the chronic phase in a patient with complete SCI [19], our study found no significant difference in test-retest reliability between post-acute and chronic groups, both showing good to excellent reliability. This suggests that chronicity may have a limited impact on SSR stability in our study.

Strengths and limitations

The first strength of this study was that our study aimed to decrease assessment bias as a blinding interpreter (ST) about the clinical information, including the level and AIS of the

participants. This result confirms that the SSR study has good to excellent test-retest reliability itself then a development of clinically blinded SSR interpreters via artificial intelligence (AI) algorithm could be possible. Second, our study calculated the sample size and recruited more participants than the previous study (40 vs 18) [9] to confirm that the sample size would be adequate. Therefore, the test-retest reliability presented in this study should have enough power and should be reliable. Third, our study used the supraorbital nerve stimulation which might be the most appropriate stimulating site in people with SCI since it is always located above the level of SCI then adequate sympathetic stimuli should be ensured. Using median nerve stimulation in people with complete tetraplegia who have abnormal sensations in the upper extremities may deliver inadequate stimuli to induce sympathetic response. This study also excluded individuals with SCI with concomitant peripheral neuropathy by evaluating median SNAP and medial plantar CNAP, which are the nerves innervated in the skins responsible for developing hand and foot SSR and may affect the results of SSR. Finally, our study assessed the temperature of bilateral hands and feet which could be a factor affecting SSR amplitude.

The limitation of this study was, first, the sample size in some subgroups, e.g., elderly subgroup, may not be adequate, which potentially caused unprecise test-retest reliability in those groups. Second, clinical information was not blinded to the assessor (TB), which potentially led to a performance bias of the assessor while obtaining raw SSR results. A future study focusing on investigating test-retest reliability in an elderly subgroup with an adequate sample size and blinding to the SSR assessor should be needed. Finally, 65% of participants in this study had a foot SSR score of zero, which may reflect a potential floor effect due to the

use of a strict 0.05 mV amplitude cutoff. Although this threshold has been used in previous studies [9], it may limit sensitivity to small but clinically relevant responses. Future research should consider employing a graded or semi-quantitative scoring system based on response magnitude to provide a more nuanced evaluation of autonomic function.

Conclusions

SSR is a non-invasive electrodiagnostic study aiming to evaluate abnormalities in the autonomic function pathway. This study demonstrated that SSR, when induced by supraorbital nerve stimulation and evaluated using the SSR score, provides good to excellent test-retest reliability for both hand and foot responses in individuals with SCI. These findings support the use of SSR as a clinically reliable and practical tool for monitoring autonomic dysfunction in the SCI population, particularly for early detection and timely intervention in autonomic-related complications.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Author Contributions

ST and TB were responsible for designing the research question, collecting and analyzing the data, drafting the manuscript, and writing the final version of the manuscript. SP was responsible for designing the research question, analyzing the data, and commenting on the final version of the manuscript.

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Data Archiving

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Statement of Ethics

The authors certify that the protocol of this analysis was approved by the Research Ethics Committee of the study site. Methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants prior to study participation.

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Figure: 1

Table: 3

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Figure legends

Figure 1. The method of sympathetic skin response (SSR) using in this study: stimulation site = supraorbital nerve, active electrode = palmar or plantar surface of both hands and feet, reference electrode = dorsal surface of both hands and feet, and the example of SSR recording at palm and sole.

Table 1. Characteristics of the participants

Characteristics	n (%)
Gender	
Male	29 (72.5)
Female	11 (27.5)
Age (mean \pm SD, year-old)	43 \pm 15.29
18-30	9 (22.5)
31-45	12 (30.0)
46-60	13 (32.5)
61-75	6 (15.0)
Onset	
< 1 year	25 (62.5)
1-5 years	10 (25.0)
6-10 years	1 (2.5)
11-15 years	1 (2.5)
16-20 years	1 (2.5)
21-25 years	2 (5)
Etiology	
Traumatic	32 (80.0)
Non-traumatic	8 (20.0)
Level of injury	
C1-C8	18 (45.0)
T1-T3	4 (10.0)
T4-T9	8 (20.0)
T10-L2	9 (22.5)
L3-S1	1 (2.5)
AIS	
A	19 (47.5)

B	8 (20.0)
C	4 (10.0)
D	8 (20.0)
E	1 (2.5)
BMI (mean \pm SD, kg/m ²)	21.8 \pm 3.7
≤ 22 kg/m ²	23 (57.5)
> 22 kg/m ²	17 (42.5)

SD, standard deviation; AIS, American Spinal Injury Association (ASIA) Impairment Scale; BMI, body mass index

Table 2. Sympathetic skin response scores of the participants

Parameters	Mean (SD)	Median (25th, 75th percentile)	Minimum	Maximum
Hand SSR score (1 st)	2.74 (2.24)	3.5 (1, 5)	0	5
Hand SSR score (2 nd)	2.75 (2.26)	3.75 (1.25, 5)	0	5
Foot SSR score (1 st)	1.14 (1.91)	0 (0, 0.75)	0	5
Foot SSR score (2 nd)	0.96 (1.84)	0 (0, 0.38)	0	5

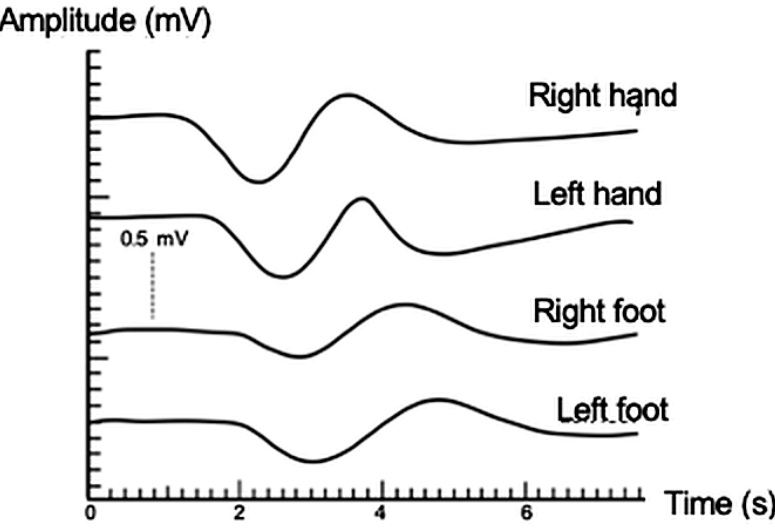
SD, standard deviation; SSR, sympathetic skin response

Table 3. Test-retest reliability of sympathetic skin response score for overall participants and participants in each subgroup

Site of SSR score	ICC	95% CI of ICC	ICC	95% CI of ICC
Overall participants (n=40)				
Hand SSR score	0.963	0.888-0.967		
Foot SSR score	0.833	0.707-0.908		
Age	< 60 years old (n=34)		≥ 60 years old (n=6)	
Hand SSR score	0.936	0.875-0.967	0.966	0.711-0.995
Foot SSR score	0.886	0.784-0.941	0.540	-0.160-0.913
BMI	≤ 22 kg/m² (n=23)		> 22 kg/m² (n=17)	
Hand SSR score	0.954	0.893-0.980	0.920	0.798-0.970
Foot SSR score	0.825	0.630-0.922	0.848	0.612-0.943
Etiology of SCI	Traumatic (n=32)		Non-traumatic (n=8)	
Hand SSR score	0.940	0.881-0.970	0.941	0.734-0.988
Foot SSR score	0.810	0.633-0.897	0.995	0.977-0.999
Level of SCI	Tetraplegia (n=18)		Paraplegia (n=22)	
Hand SSR score	0.926	0.813-0.972	0.926	0.832-0.968
Foot SSR score	0.756	0.461-0.901	0.864	0.701-0.942
Completeness of SCI	Complete (n=19)		Incomplete (n=21)	
Hand SSR score	0.905	0.770-0.962	0.974	0.936-0.989
Foot SSR score	0.801	0.552-0.919	0.844	0.660-0.933
Phase of SCI	Post-acute (< 1 year) (n=25)		Chronic (≥ 1 year) (n=15)	
Hand SSR score	0.955	0.901-0.980	0.901	0.739-0.965
Foot SSR score	0.817	0.627-0.915	0.876	0.641-0.958

SSR, sympathetic skin response; ICC, intraclass correlation coefficient; CI, confident interval; BMI, body mass index; SCI, spinal cord injury

ICC was performed using a two-way mixed effects model with an absolute agreement definition.



Supraorbital nerve stimulation site

