Assessment of Autonomic Dysfunction in Parkinson's Disease: The SCOPA-AUT

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Abstract: **We developed a questionnaire to assess autonomic symptoms in patients with Parkinson's disease (PD) and evaluated its reliability and validity. Based on the results of a postal survey in 46 PD patients, 21 multiple system atrophy patients, and 8 movement disorders specialists, items were included according to their frequency, burden, and clinical relevance. The questionnaire was evaluated in 140 PD patients and 100 controls, and test–retest reliability was established in a sample of 55 PD patients. The SCOPA-AUT consists of 25 items assessing the following regions: gastrointestinal (7), urinary (6), cardiovascular (3), thermoregulatory (4), pupillomotor (1), and sexual (2 items for men and 2 items for women) dysfunction. Test–retest reliability was good. Autonomic problems increased significantly with increasing disease severity for all autonomic regions, except sexual dysfunction. We conclude that SCOPA-AUT is a reliable and valid questionnaire that evaluates autonomic dysfunction in PD.** © 2004 Movement Disorder Society

Key words: Parkinson's disease; autonomic dysfunction; questionnaire

Parkinson's disease (PD) has mainly been characterized in terms of motor impairments. Increasingly, it has been recognized that the clinical spectrum of PD is more extensive, including also cognitive, mood, sleep, and a broad spectrum of autonomic features involving gastrointestinal, urinary, sexual, cardiovascular, thermoregulatory, respiratory, and pupillomotor functions.[1–7] The overall prevalence of autonomic features varies considerably from 2% for urinary incontinence to 72% for constipation[8]; and in part, they have been related with disease duration, disease severity, or use of antiparkinsonian drugs.[9,10] Autonomic dysfunction in PD patients is a serious problem, it is associated with depression and impacts on daily functioning and quality of life.[11,12] For several autonomic symptoms, including gastrointestinal and urinary problems, orthostatic hypotension, and erectile dysfunction, therapeutic interventions have become available.[13,14]

Despite a great deal of research, no reliable and valid instrument exists that encompasses the full spectrum of autonomic problems, thus, the primary aim of this study was to develop a reliable and valid questionnaire for autonomic dysfunction in PD. Autonomic failure is also a frequent and prominent manifestation of multiple system atrophy (MSA).[15] Although the profile of autonomic features is quite similar, autonomic dysfunction is more severe in MSA.[16] Therefore, the scale was designed to reflect autonomic features in MSA as well. The development of the SCOPA-AUT is part of a larger research project, the SCales for Outcomes in PArkinson's disease (SCOPA), in which practical and clinimetric sound instruments for all relevant regions in PD are selected or developed.

MATERIALS AND METHODS

The first phase consisted of the development of the questionnaire, and in the second phase, we did a clinimetric evaluation of the SCOPA-AUT. The local medical ethics committee approved the study protocol.

Development of the SCOPA-AUT

Items were selected by an extensive review of the literature on autonomic symptoms in PD and MSA, and by consulting clinicians specializing in neurophysiology, gastroenterology, gynaecology, urology, and sexology. Sleep disturbances are common in PD and may have various causes, including autonomic dysfunction. Due to the complexity of sleep, this aspect was not incorporated in the SCOPA-AUT, but a separate scale addressing sleep has been developed.[17]

Each autonomic item was addressed by two questions: the frequency of the problem ("How often do you suffer from this problem?") followed by a question addressing the burden to the patient ("How much does this problem bother you?"). All questions referred to the past month, except for syncope (past 6 months). The questionnaire was piloted in 16 patients for intelligibility of questions and response options, and unclear questions were rephrased.

This initial questionnaire was sent to 55 PD patients, selected from the outpatient movement disorders clinic of the Leiden University Medical Center who fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria (UKPDSBB) for idiopathic PD.[18] PD patients were selected to represent the different Hoehn and

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TABLE 1. *Subject characteristics of in the first and second postal survey (means ± SD)*

Variable	Postal survey 1		Postal survey 2		
	PD-1	MSA	PD-2	Controls	*P*
Patients (n)	46	21	140	100	—
Age (yr)	64.9 ± 9.2	63.9 ± 8.0	65.6 ± 10.9	61.4 ± 11.2	0.005[1]
Gender (M/F)	26/19	12/9	84/56	48/52	0.066[2]
Disease duration (yr)	10.6 ± 5.9	6.8 ± 2.7	9.9 ± 5.2		
H&Y distribution 1/2/3/4/5	3/15/15/10/1		4/53/48/25/3		

Assessment by *t* test[1] and χ^2 test[2] of the subjects in the second postal survey.
PD, Parkinson's disease; MSA, multiple system atrophy; H&Y, Hoehn and Yahr.

Yahr (H and Y) stages.[19] The questionnaire was also sent to 18 MSA patients of the same clinic who fulfilled the criteria for MSA,[20] and to 20 MSA patients who attended a MSA meeting organized by the Dutch Parkinson's Disease Society. Nonresponders were reminded 2 weeks later. Ten movement disorder specialists were contacted to rate the clinical relevance of the items.

The mean, standard deviation (SD), and frequency distribution of each item was calculated for the frequency and the burden of the problem, as well as the product of frequency and burden. For either PD or MSA patients, items were selected with high frequency, high burden, a combination of high frequency and burden, or high clinical relevance as judged by the specialists. Redundant items (interitem correlation above 0.80) were removed.

The selected items were rephrased into a single question evaluating the frequency of the problem, with four comprehensible response options ranging from 0 ("never") to 3 ("often"). The urinary and sexual regions have an additional response option, to indicate whether a subject used a catheter or had not been sexually active, respectively. The second questionnaire was again piloted for clearness and wording in 10 patients, and ambiguous or misleading questions were rephrased.

Evaluation of the SCOPA-AUT

A second postal survey was sent to 185 PD patients fulfilling the UKPDSBB criteria for idiopathic PD and 112 controls. To ensure sufficient numbers of patients in all disease stages, 11 PD patients in H and Y stages 4 and 5 participated in both studies. This strategy was not expected to bias the results, because all items had been rephrased and the time interval between the two questionnaires was more than 7 months. Each patient was asked to provide two age-matched controls; partners were not allowed as control subjects. The postal survey also included demographic questions and a questionnaire on comorbid diseases (assessing 20 common chronic disorders).[21] Information on disease severity, disease duration, and medication was obtained by chart review. Nonresponders were reminded 2 weeks later. The first 60 PD patients returning the questionnaire received a second mailing for the assessment of the test–retest reliability.

The median and frequency distribution of each item was calculated. Differences in items between the two groups were analyzed using the Mann–Whitney *U* test. Items that did not discriminate between the PD and control group were removed from the questionnaire, provided this removal did not threaten the content validity. Test–retest reliability for items was assessed with a weighted kappa (K_w, quadratic weights). Means ± SD were calculated for the total and region scores, and differences between the two groups were analyzed using a Students *t* test for independent samples. Test–retest reliability for the total and region scores was analyzed using an intraclass correlation coefficient (ICC). Known-group validity was examined by comparing the SCOPA-AUT total and region scores between controls and patients and between controls and patients grouped by modified H and Y stages (mild, moderate, severe), using analysis of variance, post hoc *t* tests with Bonferroni correction, Kruskal–Wallis test, and ordinal regression. Spearman correlations were used to assess the correlation between the SCOPA-AUT total and region scores and disease duration, disease severity, and dose of levodopa.

RESULTS

Development of the SCOPA-AUT

A total of 45 items in the following regions were selected for the questionnaire: gastrointestinal (13), urinary (8), cardiovascular (5), thermoregulatory (6), pupillomotor (1), skin (1), respiratory (2), and sexual (6 for men and 3 for women) dysfunction. An additional item assessed the use of medication in the aforementioned regions. Forty-six PD patients returned the questionnaire from the first postal survey, a response rate of 84%. The mean ± SD age of the patients was 64.9 ± 9.2 years, and the disease duration 10.6 ± 5.9 years (Table 1). Twenty-one MSA patients returned the questionnaire, a response

TABLE 2. *Items deleted from the SCOPA-AUT*

Item
Retrosternal pain
Persistent abdominal fullnes
Bloating
Straining to urinate
Hesitancy in starting urination
Postprandial hypotension
Avoidance of standing
Seborrhea
Hypohydrosis
Flushing
Nocturnal erections
Erectile rigidity
Ability to maintain an erection
Absence of emission
Vaginal pain during sexual intercourse
Snoring
Sleep apnea

rate of 53%. The mean ± SD age of the MSA patients was 63.9 ± 8.0 years, and the disease duration 6.8 ± 2.7 years. Of the 10 movement disorder specialists, 8 returned the questionnaire. Based on the results of the patients with PD and MSA, 23 and 24 items, respectively, fulfilled the criteria of frequency, burden, and product of both, resulting in a total of 25 items. The specialists indicated clinical importance for 10 additional items. We aimed for a balanced representation of items on sexual dysfunction for both sexes. Therefore, the item "problem with orgasm," that did not meet the criteria in the women's group, was retained for reasons of content. Eight items were removed because of redundancy. Overall, in the item selection process, 17 items were removed (Table 2), and a total of 28 items remained in the following regions: gastrointestinal (10), urinary (6), cardiovascular (3), thermoregulatory (4), pupillomotor (1), and sexual (2 for men and 2 for women) dysfunction.

Evaluation of the SCOPA-AUT

In the second postal survey, 143 of the 185 PD patients returned a questionnaire, a response rate of 77%. Three PD patients were excluded from the analyses because more than 20% of their data was missing. The response rate for the test–retest assessment was 92%. Two PD patients were excluded from this analysis because more than 20% of their data were missing. The response rate in the control group was 93%. There were no differences between the characteristics of the total PD group and the sample used for the test–retest reliability. Compared to the PD patients, the subjects in the control group were significantly younger and included more women (Table 1). The analyses, therefore, were adjusted for age and sex.

Few missing data were low, namely 0 to 1% per item in the control group and 0 to 4% in the PD group, except for the questions regarding sexual dysfunction, which had the most missing values, especially in female PD patients (11–13%). In total, 46 to 50% of the women with PD and 39 to 40% of the women in the control group scored "not applicable" on these items, compared to 21 to 24% of the male PD patients and 10 to 17% of the men in the control group. Women who had missing values in the sexual dysfunction region or who scored "not applicable," were significantly older, both in the PD and in the control group.

Test–retest reliability for the individual items was high; K_w ranged from 0.45 to 0.90 (Table 3). According to the criteria of Landis and Koch,[22] two items had only moderate agreement (K_w between 0.41 and 0.60): "frequency" (0.45), and "faecal incontinence" (0.56). Compared to controls, PD patients had significantly higher scores on all items ($P < 0.05$), except for the items "gastric acid," "diarrhea," "flatulence," and "syncope." Similar results emerged when the analysis was corrected for age, or when analyzed separately for men and women. Compared to controls, PD patients had a significantly higher use of medication for constipation (23% vs. 4%). The items "gastric acid," "diarrhea," and "flatulence" were removed because the remaining seven items still covered the content of the region of gastrointestinal dysfunction adequately, whereas "syncope" was retained for reasons of content. The final version of the questionnaire included 25 items (Appendix), with the total score ranging from 0 to 69, higher scores reflecting worse autonomic functioning.

The ICC for the total score was 0.87 and the region scores ranged from 0.65 to 0.90 (Table 4). PD patients had significantly higher scores than control subjects on all regions except for items addressing sexual dysfunction in men and women (Table 4). Total and region scores showed significant differences between groups based on H and Y stages, except for sexual dysfunction in women (Table 5). A significant trend was present for these regions (again except for sexual dysfunction) with more autonomic problems in patients with more advanced PD. The Spearman correlation between the total score and H and Y stage was 0.60 ($P < 0.01$), ranging from 0.20 to 0.70 for the regions. There were no significant correlations between the total or region scores with disease duration or dose of levodopa. In the study participated 22 de novo PD patients, who scored significantly higher than controls on the total and region scores. There were no differences in the scores between severely affected PD patients who participated in both the first and second postal survey and those who participated in the second postal survey only.

TABLE 3. *Test–retest reliability in PD, median and presence of symptoms (% ≥1) in the PD and control group (second survey)*

Item	PD			Controls	
	K_w*	Median	%	Median	%
Swallowing/choking	0.69	1	61	0	20
Sialorrea	0.86	1	76	0	9
Dysphagia	0.74	0	40	0	11
Early abdominal fullnes	0.73	1	51	0	27
Gastric acid	0.90	0	32	0	29
Constipation	0.75	1	54	0	11
Straining for defacation	0.74	1	83	0	40
Faecal incontinence	0.56	0	14	0	3
Diarrhea	0.77	0	20	0	28
Flatulence	0.80	1	73	1	68
Urgency	0.79	1	68	0	21
Urinary incontinence	0.84	0	48	0	26
Incomplete emptying	0.69	1	55	0	28
Weak stream of urine	0.87	1	65	0	33
Frequency	0.45	1	90	1	77
Nocturia	0.76	2	91	2	89
Light-headed when standing up	0.75	1	51	0	15
Light-headed when standing for some time	0.69	0	38	0	10
Syncope	0.85	0	5	0	1
Hyperhidrosis during the day	0.73	1	52	0	31
Hyperhidrosis during the night	0.80	1	63	0	40
Cold intolerance	0.74	0	44	0	25
Heat intolerance	0.74	1	53	1	52
Oversensitive to bright light	0.74	1	61	0	32
Men: erection problem	0.87	1	60	0	37
Men: ejaculation problem	0.73	1	57	0	43
Women: vaginal lubrication	0.77	0	48	1	52
Women: problem with orgasm	0.61	1	68	0	47

*K_w, weighted kappa statistic.
PD, Parkinson's disease.

PD patients recorded more comorbid diseases than subjects in the control group. However, some of these comorbidities may be results from autonomic dysfunction in PD: dizziness, urinary incontinence, and bowel dysfunction. After the removal of these symptoms from the comorbidity questionnaire, no differences emerged between the groups.

DISCUSSION

This study confirms that autonomic dysfunction is a prominent aspect of PD, being present early in the disease and increasing with advancing H and Y stages. Although some studies have reported the use of a questionnaire to assess autonomic dysfunction, these questionnaires were

TABLE 4. *Autonomic regions and the total score of the PD and control group, and test–retest reliability in the PD group*

Region	PD	Control	*P*	ICC*
Gastrointestinal dysfunction (7)	5.3 ± 3.1	1.4 ± 1.6	0.000[a]	0.90
Urinary dysfunction (6)	7.1 ± 4.2	3.9 ± 2.4	0.000[a]	0.83
Cardiovascular dysfunction (3)	1.2 ± 1.3	0.3 ± 0.6	0.000[a]	0.83
Thermoregulatory dysfunction (4)	3.1 ± 2.4	1.8 ± 2.0	0.000[a]	0.82
Pupillomotor dysfunction (1)	0.9 ± 0.9	0.4 ± 0.7	0.000[b]	0.74[c]
Sexual dysfunction (2 + 2)	1.9 ± 1.8	1.3 ± 1.6	0.035[a]	—
Sexual dysfunction men (2)	2.0 ± 1.9	1.3 ± 1.7	0.055[a]	0.84
Sexual dysfunction women (2)	1.7 ± 1.5	1.4 ± 1.5	0.440[a]	0.68
Total autonomic score (23)	18.8 ± 8.5	8.8 ± 5.4	0.000[a]	0.87

Values are expressed as mean ± SD; unless otherwise indicated.
*Intraclass correlation coefficient;
[a]*t* test; [b]Mann–Whitney *U* test; [c]Weighted kappa statistic.
PD, Parkinson's disease.

TABLE 5. *Known-groups comparisons of total and region scores between controls and patients grouped by Hoehn and Yahr stage*

Region	Controls	Mild*	Moderate*	Severe*	*P*	Trend**
Gastrointestinal dysfunction	1.4	4.4	5.7	6.9	0.000[a]	+
Urinary dysfunction	3.9	6.2	7.5	8.1	0.000[a]	+
Cardiovascular dysfunction	0.3	1.0	1.2	1.1	0.000[a]	+
Thermoregulatory dysfunction	1.8	3.1	3.1	3.9	0.000[a]	+
Pupillomotor dysfunction	0.4	0.8	0.9	0.8	0.000[b]	+
Sexual dysfunction	1.3	1.6	2.3	1.5	0.055[a]	−
Sexual dysfunction men	1.3	1.6	2.6	1.5	0.062[a]	−
Sexual dysfunction women	1.4	1.4	1.8	1.6	0.890[a]	−
Total autonomic score	8.8	16.5	19.8	21.4	0.000[a]	+

*Mild = H&Y 1 + 2; moderate = H&Y 3; severe = H&Y 4 + 5.
[a]ANOVA.
[b]Kruskal–Wallis test.
**Trend, +/− indicates that a significant trend is/is not present ($P \leq 0.05$), all models have good fit.
ANOVA, analysis of variance; H&Y, Hoehn and Yahr.

never thoroughly validated.[23] Selection of SCOPA-AUT items was based on patient response criteria for frequency and burden and clinical relevancy as judged by specialists. The response rates of the two postal surveys were high, which may indicate the importance of these aspects to patients.

As no gold standard or validated questionnaire for autonomic dysfunction in PD exists, our approach of developing the SCOPA-AUT was focused on the content and the clinical applicability of the questionnaire. The content validity of the SCOPA-AUT is good, based on opinions of experts and patients. One may question if items such as problems with swallowing, sialorrhea, and dysphagia reflect pure autonomic symptoms or motor impairments of PD, but we decided to include these items to cover the whole spectrum of problems within the alimentary tract.[1] Some of the symptoms in the SCOPA-AUT could be side effects of medication instead of symptoms of the disease itself. However, we found no relation between the dose of L-dopa and autonomic dysfunction, and even de novo patients indicated significantly more autonomic dysfunction than controls.

The instrument shows good known-groups validity, as it adequately discriminates between PD patients and controls and between controls and PD groups of mild, moderate, and severe disease stages. The test–retest reliability is very high, both for the total and regions score and the individual items. In clinical management, the neurologist could use the questionnaire (completed by the patient at home) to screen for autonomic regions that require more specific attention during the visit. Additionally, the scale could be used in trials to assess the changes in autonomic dysfunction.

In agreement with other studies,[24] the questions on sexual dysfunction had the most missing values, 13% in female PD patients (in addition to 50% answering "not applicable"). Only a small sample of women, thus, could be used for analysis, revealing no differences in sexual dysfunction between patients and controls. Women who did not answer these questions were significantly older than responding women. Therefore, the results may be different in a younger sample.

To capture the spectrum of autonomic dysfunction in PD adequately, we aimed to include sufficient numbers of PD patients of each H and Y stage. Eleven patients in H and Y stages 4 and 5 were included in the second postal survey who had also participated in the first postal survey. A potential bias of including these patients was considered small as the time interval between both surveys was at least 7 months and all items had been rephrased. This finding was confirmed by a post hoc analysis showing no differences in the scores of the two groups of severely affected PD patients.

PD patients had significantly higher scores than controls, for the total score, most regions and most items. This is not in agreement with other studies, where only some of these symptoms were found to be significantly different from those of controls.[23,25] This discrepancy may be explained by the large size of our PD and control sample and the broad range of PD patients regarding disease severity and duration. Within the PD group, patients with more advanced disease stages also had higher region scores, except for sexual dysfunction. This finding indicates that the questionnaire may have the ability to measure change, although responsiveness was not assessed in this study. Longitudinal studies of disease progression or the evaluation of effective treatment are needed to evaluate this property of the questionnaire.

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APPENDIX
SCOPA-AUT

The response options are for all questions: *never, sometimes, regularly, often.* In some regions extra response options are added. The questions concerning medication have the response options: *no* and *yes*.

1. In the past month have you had difficulty swallowing or have you choked?
2. In the past month, has saliva dribbled out of your mouth?
3. In the past month, has food ever become stuck in your throat?
4. In the past month, did you ever have the feeling during a meal that you were full very quickly?
5. *Constipation is a blockage of the bowel, a condition in which someone has a bowel movement twice a week or less.* In the past month, have you had problems with constipation?
6. In the past month, did you have to strain hard to pass stools?
7. In the past month, have you had involuntary loss of stools?
8. In the past month, have you had difficulty retaining urine? *(Extra: use catheter)*
9. In the past month, have you had involuntary loss of urine? *(Extra: use catheter)*
10. In the past month, have you had the feeling that after passing urine your bladder was not completely empty? *(Extra: use catheter)*
11. In the past month, has the stream of urine been weak? *(Extra: use catheter)*
12. In the past month, have you had to pass urine again within 2 hours of the previous time?*(Extra: use catheter)*
13. In the past month, have you had to pass urine at night? *(Extra: use catheter)*
14. In the past month, when standing up have you had the feeling of becoming either light-headed, or no longer being able to see properly or no longer being able to think clearly?
15. In the past month, did you become light-headed after standing for some time?
16. Have you fainted in the past 6 months?
17. In the past month, have you ever perspired excessively during the day?
18. In the past month, have you ever perspired excessively during the night?
19. In the past month, have your eyes ever been oversensitive to bright light?
20. In the past month, how often have you had trouble tolerating cold?
21. In the past month, how often have you had trouble tolerating the heat?

The following 3 questions are only for men:

22. In the past month, have you been impotent (unable to have or maintain an erection)? *(Extra: not applicable)*
23. In the past month, how often have you been unable to ejaculate? *(Extra: not applicable)*

23a. In the past month, have you taken medication for an erection disorder? (If so, which medicine?)

(no; yes: _____)

The following 2 questions are only for women:

24. In the past month, was your vagina too dry during sexual activity? *(Extra: not applicable)*
25. In the past month, have you had difficulty reaching an orgasm? *(Extra: not applicable)*

The following questions are for everyone:

26. In the past month, have you used medication for:

a. constipation? b. urinary problems? c. blood pressure? d. other symptoms*(no; yes: _____)*

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Elevated Threshold for Intracortical Inhibition in Focal Hand Dystonia

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Abstract: **Differences between control and focal hand dystonia (FHD) subject groups in short interval intracortical inhibition (SICI) as determined by paired transcranial magnetic stimulation (TMS) can be difficult to demonstrate, due to interindividual differences. The purpose of this study was to compare two TMS methods for assessing SICI in 8 control and 7 FHD subjects. Electromyographic (EMG) data were recorded from the first dorsal interosseous (FDI) muscle of the dominant hands of the control subjects and affected hands of the FHD subjects. The first method used a conventional approach of setting conditioning stimulus intensity to 80% of rest threshold (RTh) and test stimulus intensity to 120% RTh. Three interstimulus intervals (ISIs) were used: 2 msec, 3 msec, and the ISI between 2 and 3 msec that produced optimal SICI. The second method was novel in that test stimulus intensity was set to 150% active threshold (ATh), and conditioning stimulus intensity was varied between 50% and 100% ATh. The latter was determined at the threshold for SICI and expressed as a ratio of ATh. There was no difference between the subject groups in the degree of SICI produced using the first method, at the three ISIs studied. However, using the second method, the SICI threshold:ATh ratio was found to be significantly higher for FHD subjects. This finding suggests that determining the SICI threshold:ATh ratio may be a more sensitive measure of intracortical inhibitory function than more conventional methods.** © 2004 Movement Disorder Society

Key words: intracortical inhibition; transcranial magnetic stimulation; focal hand dystonia

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When a suprathreshold magnetic (test) stimulus is preceded by a subthreshold magnetic (conditioning) stimulus, the resulting motor evoked potential (MEP) is either inhibited or facilitated, depending upon the interstimulus interval (ISI).[1] Generally, short ISIs (1–5 msec) produce inhibition of the test MEP, whereas longer ISIs (10–15 msec) produce facilitation of the test MEP.[1,2] These authors also demonstrated that inhibition of the test MEP amplitude was maximal when the target muscle was at rest, and the conditioning stimulus intensity was set to between 70% and 90% of rest threshold (RTh).[1] The conditioning stimulus is thought to excite γ-aminobutyric acid (GABA)-ergic intracortical inhibitory interneurons, which inhibit corticospinal cells with a latency of between 1 and 5 msec.[3,4] Other authors have shown that even minimal levels of voluntary activation of the target muscle significantly reduce the degree of inhibition produced by subthreshold conditioning stimuli delivered at ISIs between 1 and 6 msec.[5–7] This finding is probably due to reduced excitability of the inhibitory interneurons that project to the corticospinal neurons responsible for activation of the target muscle.[5]

Recently, Fisher and colleagues (2002) demonstrated that the short interval intracortical inhibition (SICI) produced with an ISI of 1 msec is functionally distinct from that produced with an ISI of 2 to 3 msec. When the ISI is set to 2.5 msec, the threshold conditioning stimulus intensity that produces inhibition is approximately 56% RTh, and inhibition is completely abolished by voluntary activation of the target muscle. In contrast, when the ISI is set to 1 msec, the threshold conditioning stimulus intensity that produces inhibition is lower (around 42% RTh), and inhibition is much less affected by voluntary activation of the target muscle. These authors suggest that the conditioning stimulus produces refractoriness of cortical axons with an ISI of 1 msec, which recovers by 2.5 msec.[8]

This finding has since been supported by Hanajima and coworkers (2003), who investigated the effects of different ISIs upon the early (I1) and late (I3) waves that descend along the corticospinal pathway in response to transcranial magnetic stimulation (TMS). These authors found that, at ISIs of 3, 4, and 5 msec, the conditioning stimulus inhibited only the I3 waves, whereas at an ISI of 1 msec inhibition of both I1 and I3 waves, as well as magnetically evoked direct (D) waves, was observed. Furthermore, none of these components were inhibited with an ISI of 2 msec. These findings support those of Fisher and colleagues (2002) by demonstrating differences in the inhibition produced at an ISI of 1 msec and that produced with longer ISIs. Hanajima and coworkers (2003) suggest that the SICI observed with ISIs of 3 to 5 msec is due to GABAergic synaptic activity within M1