Review

GIN Test: A Meta-Analysis on Its Neurodiagnostic Value

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Renata Filippini*
Bryan Wong†
Eliane Schochat*
Frank Musiek†

Abstract

Purpose: A meta-analysis was conducted to evaluate how effective the Gaps-in-Noise (GIN) test is in separating populations who are and who are not at risk of having neurological damage related to the central auditory nervous system (CANS). This was investigated by asking three specific questions: (1) Does ear and side of lesion have an effect over the individual's performance? (2) How large is the difference in performance between control and neurological groups? (3) What are the diagnostic indices related to the GIN test?

Data Collection and Analysis: A literature review was performed between April 2016 and April 2017. The eligibility criteria for inclusion were as follows: (1) studies that used the GIN test as an outcome measure, (2) studies that included adult participants who either had confirmed lesions or were at risk of having lesions to the CANS or related regions, and (3) studies that had a neurologically normal control group. From relevant studies that met eligibility criteria, information regarding study design, participants, lesion details and origins, use of additional assessments, GIN performance scores for both control (CTRL) and neurological (NRLG) groups, GIN cutoff scores and proportion of individuals with normal and abnormal performances were all included.

Results: Nine studies were included, totaling 221 participants in NRLG (stroke = 90, epilepsy = 67, and blast exposure [BLST] = 64) and 262 in CTRL (Stroke = 106, Epilepsy = 98, and BLST = 58). No significant ear effects related to side of lesion were observed for the GIN test in neurological patients nor were there significant ear differences for normal individuals with symmetrically normal hearing. The GIN demonstrated consistency among different neurological populations, presented good sensitivity and specificity rates, and was overall accurate in discriminating between participants with neuroauditory lesions from neurologically normal individuals.

Conclusions: The GIN is thus a clinically effective measure that provides insight into the CANS integrity and may aid in clinical diagnosis by distinguishing between populations who are and who are not at risk of having neurological damage affecting the CANS.

Key Words: auditory perceptual disorders, Gaps-in-Noise, meta-analysis, nervous system diseases, sensitivity and specificity

Abbreviations: AP = auditory processing; BLST = blast exposure; CANS = central auditory nervous system; CTRL = control; DOR = diagnostic odds ratio; EPLS = epilepsy; ES = effect size; FN = false negatives; FP = false positives; GDT = gap detection thresholds; GIN = Gaps-in-Noise; LE = left ear;

*Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil; †Speech, Language, and Hearing Department, University of Arizona, Tucson, AZ

Corresponding author: Renata Filippini, Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil; Email: refilippini@usp.br

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LSL = left side lesion; NLR = negative likelihood ratios; NRLG = neurological; PLR = positive likelihood ratios; RE = right ear; RSL = right side lesion; SD = standard deviations; STRK = stroke; TBI = traumatic brain injury; TN = true negatives; TP = true positives; 95% CI = 95% confidence interval

The Gaps-in-Noise (GIN) test was developed in the early 2000s, with the intent to be a clinically feasible test for temporal resolution ability. The test, which involves the perception of silent intervals of varying durations embedded in a noise burst, was an alternative to the traditional psychoacoustic gap detection procedures (Musiek et al, 2005). These traditional paradigms tended to have long completion times and need complex instrumentation interfaces that made them difficult to use in a clinical setting (Hoover et al, 2015).

After the first validation study conducted by Musiek et al (2005), an impressive body of research has emerged, evaluating its clinical utility and application. The GIN performance was investigated for normal individuals of all ages (Samelli and Schochat, 2008; Shinn et al, 2009; Amaral and Colella-santos, 2010; Humes et al, 2010; John et al, 2012; Majak et al, 2015), as well as for patients with neurological and/or developmental disorders (Zaidan and Baran, 2013; Boscariol et al, 2015), cognitive decay (Iliadou et al, 2017), and patients exposed to blasts or toxic substances (Zamyslowska-Szmytke et al, 2009; Bazilio et al, 2012), among others.

Studies in the normal population have consistently shown similar average performance regardless of spoken language (Murphy et al, personal communication). The GIN test has also been shown to have good test–retest reliability (Musiek et al, 2005) and to suffer less influence of cognition and higher order language abilities (Tomlin et al, 2015; Murphy et al, personal communication). Studies comparing different paradigms have shown that the traditional adaptive gap detection threshold (GDT) paradigms elicited smaller GDT in normal individuals compared with the GIN test–approximated thresholds. Despite this, thresholds in both paradigms were significantly correlated (Hoover et al, 2015; Wong and McPherson, 2015), which speaks in favor of using the GIN test in a clinical setting given its shorter completion time and its ease of administration.

For a test to be clinically useful, it must be validated using a gold standard population and also show a good efficacy rate. It is recommended that the gold standard population for auditory processing (AP) deficits should be individuals with neurological lesions affecting the central auditory nervous system (CANS) (ASHA, 2005; AAA, 2010). Although not all individuals with AP deficits (especially children) have clear and confirmed neurological lesions to the CANS, one can expect that dysfunctions at this level may be correlated to dysfunctions observed in patients with neurological lesions in the CANS (Weihing et al, 2015). In the aforementioned, Musiek et al (2005) and several subsequent studies verified the performance of the GIN test on different neurological populations. Therefore, the primary question posed and to be addressed is how efficient is the GIN test in discriminating patients with neuroauditory lesions from normal participants?

The purpose of this study was to examine the literature on the GIN test and evaluate its efficacy in separating populations who are and who are not at risk of having neurological damage related to the CANS. The aim was not to imply that the GIN test can diagnose any one central pathology in particular, but to substantiate the GIN test's diagnostic capability in contributing to the overall medical diagnosis while also providing researchers and clinicians with scientific evidence of its value in assessing neurologically based Central Auditory Processing Disorder.

METHODS

A literature review was performed between April 2016 and April 2017 using PubMed, MEDLINE, CINAHL, and personal reference databases. The following search terms from the title or abstract were used in different combinations: GIN, gap detection, temporal resolution, neurological patient, brain lesion, brain damage, stroke, traumatic brain injury (TBI), epilepsy, temporal lobe epilepsy, mesial temporal sclerosis. The flowchart for the bibliography search is presented on Figure 1.

The abstracts were read independently by two judges (first and second authors), considering the following eligibility criteria: use of the GIN test (Musiek et al, 2005) as an outcome measure, inclusion of adult participants who had confirmed or were at risk of having lesions to the CANS or related regions, and studies with a neurologically normal control group. The judges agreed on all the articles that met the eligibility criteria and then went on to read these articles in full to identify those that could be included in the final review. When the two judges did not agree on the inclusion of an article, the last author acted as the third judge. Finally, all included articles were either at a moderate level or high level according to the GRADE approach (Schünemann et al, 2013).

The main question proposed in this study will be investigated via three specific questions: (a) Does ear and side of lesion have an effect over the individual's performance? (b) How large is the difference in performance between control and neurological groups? (c) What are the diagnostic indices related to the GIN test?

To answer these questions, the following information was derived from the included studies: study design, participant demographics, lesion details and origins, additional assessments included on the study protocol, GIN performance for control (CTRL) and neurological (NRLG) groups, GIN cutoff scores, and the proportion of individuals

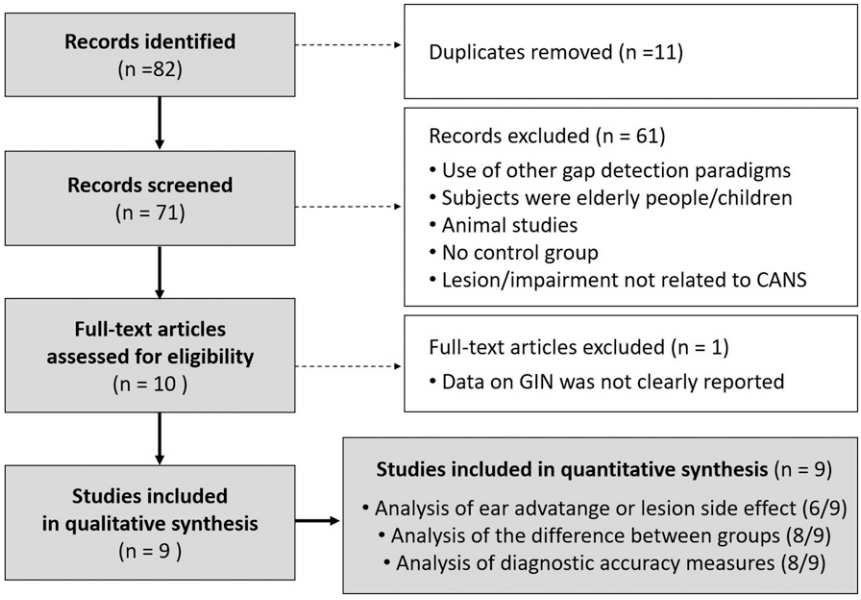

Figure 1. Flowchart of the literature search showing the four levels of search: identification, screening, eligibility, and inclusion.

with normal and abnormal performances. When this information was not clearly stated in the text, it was reported on a graph, on supplemental material, on the original dissertation, or requested directly from the authors themselves. Also, because some of the included studies reported either pooled or individual ears, the authors of the present study used either the raw data or pooled mean and standard deviations (SD) to derive the necessary information.

Effect size (ES) (i.e., Cohen's d) was calculated for each study to investigate the difference in performance between CTRL and NRLG groups, between right ear (RE) and left ear (LE), and to examine the effect of lesion side on the performance of ears ipsilateral and contralateral to the corresponding lesion. Based on each study's cutoff score, the proportion of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) were gathered or calculated. For each individual study and the overall studies, the sensitivity, specificity, positive, and negative likelihood ratios (PLR and NLR, respectively), and diagnostic odds ratio (DOR) were calculated with a 95% confidence interval (CI). See Table 3 for definitions on each of the aforementioned indices.

The software "Open Meta Analyst" (Wallace et al, 2012) was used to calculate the ES for the mean differences of group performance and ear performance, as well as the set of aforementioned diagnostic measures. Statistical heterogeneity among the studies (i.e., variability in the effects of neurological lesions to GIN performance among studies) was investigated through Cochran's Q and I^2 index. A bivariate model was used for the meta-analysis of sensitivity and specificity, and a random effects model under a DerSimonian–Laird or Sidik-Jonkman approach was used for the other meta-analysis performed here.

RESULTS

At first, 82 studies were identified using the chosen key words. After removing duplicated records and excluding those that did not fit the proposed criteria, only ten articles remained for full reading and assessment. From these, one study was excluded because GIN data were only reported via box-plot graphs, and thus, mean and SD values could not be reliably derived. Finally, a total of nine studies were included (Figure 1). It is important to note that not all nine studies were included in all three analyses because not all studies reported on the necessary information for calculation.

The nine studies included in this review are detailed in Table 1. The studies came from six countries and investigated performance on GIN from speakers of four different native languages. All studies were observational, case-controlled, and sampled by convenience. From these, GIN thresholds were observed in four studies comprising individuals with CANS lesions related to strokes (STRK) (Musiek et al, 2005 [1]; Bamiou et al, 2006 [2]; Bamiou et al, 2012 [5]; Jafari et al, 2016 [7]), three studies with individuals who had epilepsy (EPLS) (Aravindkumar et al, 2012 [3]; Rabelo et al, 2015 [6]; Lavasani et al, 2016 [8]), and two studies with individuals exposed to blast explosions (BLST) (Gallun et al, 2012 [4]; Gallun et al, 2016 [9]). In six studies, the NRLG group had confirmed lesions to either the CANS or related areas and also contained information detailing the areas and side of lesion. Study [8] was not clear on the participants having confirmed lesions, but they reliably described epileptic foci related to the CANS, which frequently lead to neurological dysfunctions and/or lesions. In studies [6] and [9], participants also

Table 1. Summary of the Studies Included in the Present Review

Study Details	Population	Sample		Hearing Assessment	Cognitive Assessment	Handedness	Medication
		N	Age				
[1] Musiek et al, 2005, USA	Stroke: confirmed lesions in auditory-related cortical and brainstem structures	NRLG = 18 CTRL = 50	46.7 ± 11 (20–65) 24.6 (18–46)	≤20 dB HL (0.25–8 kHz); symmetric	NR NR	R R	NR -
[2] Bamiou et al, 2006, UK	Stroke: confirmed acute lesion in the insula with and without involvement of adjacent cortical and subcortical areas	NRLG = 8 CTRL = 8	64.6 ± 15.3 (36–79) Matched	≤30 dB HL (0.5–4 kHz); symmetric	4 participants ABN performance in 2+/10 tests NR	R R	NR -
[3] Aradvindkumar et al 2012, India	Temporal lobe epilepsy: confirmed mesial temporal sclerosis	NRLG = 26 CTRL = 50	28.4 ± 7.4 36 ± 5.2	≤25 dB HL (0.25–8 kHz);	MMSE > 23 Unclear	R Unclear	2+ for epilepsy -
[4] Gallun et al, 2012, USA	Blast exposure: no confirmed lesion, diagnosed mild TBI (N = 19)	NRLG = 36 CTRL = 29	32.8 (20–54) 32.1 (19–54)	<50 dB HL (0.5–4 kHz); DPOAE NL	NR NR	NR NR	1+ for other injuries
[5] Bamiou et al, 2012, UK	Stroke: confirmed acute stroke of the central auditory pathway	NRLG = 21 CTR = 23	61 ± 16 (29–81) 56 ± 19 matched	<40 dB HL 1 kHz	NR NR	NR Matched	NR -
[6] Rabelo et al, 2015, Brazil	Temporal lobe epilepsy: confirmed mesial temporal sclerosis	NRLG = 16 CTRL = 30	28.9 ± 9.3 24.9 ± 3.3	≤20 dB HL (0.25–8 kHz); symmetric	NR NR	NR NR	NR -
[7] Jafari et al, 2016, Iran	Stroke: confirmed chronic lesion (MRI) to the auditory cerebrum (±adjacent areas), involvement of the MCA and/or its branches	NRLG = 45 CTRL = 25	52.2 ± 10 (36–68) 50.5 ± 9.6 (38–71)	≤20 dB HL (0.25–8 kHz); symmetric	NL (MMSE) NL IQ (RPM) Unclear	R R	NR -
[8] Lavasani et al, 2016, Iran	Temporal lobe epilepsy: epileptic foci are well described, but it is not clear if individuals have confirmed lesion related to epilepsy	NRLG = 25 CTRL = 18	31.1 (20–50) 29.4 matched	≤20 dB HL (0.25–8 kHz); symmetric	NR NR	R R	1+ for epilepsy -
[9] Gallun et al, 2016, USA	Blast exposure: no confirmed lesion, diagnosed mild TBI (N = 17)	NRLG = 28 CTRL = 29	37.3 ± 11.5 39.2 ± 13.9	≤35 dB (0.5–4 kHz); symmetric	MMSE ≥ 24 MMSE ≥ 24	NR NR	NR -

Note: NL = normal; NR = not reported; R = right.

did not have lesions confirmed by imaging techniques but were confirmed to have been exposed to blast explosions with a large number of individuals presenting a mild TBI.

The number of participants included in the NRLG groups varied between 8 and 45 participants (24 ± 10) and in the CTRL groups between 8 and 50 participants (30 ± 14), totaling 221 participants in NRLG (STRK = 90, EPLS = 67, and BLST = 64) and 262 in CTRL (STRK = 106, EPLS = 98, and BLST = 58). Participant ages varied between 18 and 81 years, with pooled mean age of 41 and 36 years for NRLG and CTRL groups, respectively. Elderly participants were included in four studies [1, 2, 5, and 7], but only studies [2] and [5] had a significant number of them. For both studies, CTRL was age-matched in relation to NRLG; therefore, any differences in performance between groups cannot be accounted by age. Large differences between NRLG and CTRL groups regarding age were observed only in study [1]. Such difference resided in the fact that the NRLG group had a majority of middle-age adults (≥40) and the CTRL group a majority of younger adults (<40). Because this is an age difference that has not yet been consistently shown to influence performance on gap detection (Lister et al, 2002; Helfer and Vargo, 2009), the study was kept in this review.

Five studies reported pure-tone audiometry within normal limits (20–25 dB; 250–8000 Hz) as inclusion criteria for both groups, whereas the other four studies also included participants with mild hearing loss between 500 and 4000 Hz. Symmetric hearing and normal tympanometry, acoustic reflexes, speech recognition test, and otoacoustic emissions were also cited as criteria for inclusion. The audiometric profile for both groups was only presented in three studies, none of which reported significant differences in thresholds between groups. In regard to additional information, four studies reported on cognitive assessment, five on handedness, and two on medication the individuals were taking or had taken for their condition.

Finally, eight studies reported on mean and SD for GIN performance for both ears and groups. Studies [2], [3], [7], and [8] presented results from the NRLG group separated by side of the lesion (right-side lesion [RSL]; left-side lesion [LSL]) (Table 2).

Difference between Ears: Does the Side of the Lesion Affect Ears Performance?

For CTRL groups, the ES for the difference between RE and LE performance in each study showed some variability ($-0.15 \leq d \leq 0.95$) (Figure 2A), but no significant heterogeneity among the studies was observed ($Q_{[7]} = 9.06$, $p = 0.248$; $I^2 = 22\%$). Most studies (5/8 studies) suggested a small degree of better RE performance but with no statistical significance. Overall, the meta-analysis has shown only a very small and not significant ES favoring the RE ($d = 0.11$, 95% CI = $-0.09, 0.32$; $p = 0.283$). The same analysis (e.g., RE versus LE) for the NRLG groups has shown similar results. The ES varied from −0.59 to 0.43 and most studies (6/8 studies) also suggested better, although nonsignificant, RE performance. Studies were also found to be homogenous among NRLG groups ($Q_{[7]} = 4.67$, $p = 0.701$; $I^2 = 0\%$), and a very small and nonsignificant overall ES favoring the RE was obtained for this group as well ($d = 0.09$, 95% CI = $-0.10, 0.29$; $p = 0.349$).

Table 2. Mean GDT for Control and Neurologic Groups Reported by the Included Studies

		CTRL			NRLG			RSL			LSL		
Study	Ear	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
[1]	R	50	4.9	0.93	18	8.5	4.32	*6*	*7.83*	*3.76*	*9*	*7.56*	*3.68*
	L		4.8	1.03		7.7	2.84		*6.71*	*3.76*		*7.67*	*2.59*
[2]	R	8	4	1.00	*8*	*9.63*	*2.83*	5	8	2.00	3	11	3.00
	L		5	1.00		*8*	*2.39*		9	1.00		6	2.00
[7]	R	25	6.4	1.84	*45*	*8.84*	*2.85*	25	8.32	3.21	20	9.5	2.39
	L		6.52	1.50		*8.93*	*2.64*		9.56	2.34		8.15	3.01
[3]	R	50	5.22	1.11	*26*	*8.85*	*3.09*	13	8.15	2.34	13	9.54	3.67
	L		5.06	1.00		*9*	*3.69*		7.85	3.00		10.1	4.06
[6]	R	30	4.7	1.00	16	7.4	2.90	*14*	*7.43*	*3.05*	*2*	*7*	*1.41*
	L		4.6	1.00		8.1	1.70		*8.14*	*1.83*		*8*	*0.00*
[8]	R	18	4.77	0.54	*25*	*6.84*	*2.60*	11	7.09	2.20	14	6.64	2.90
	L		5.1	0.83		*7.19*	*2.47*		7.18	2.30		7.2	2.60
[4]	R	29	3.79	1.29	36	6.03	3.20						
	L		4.28	2.10		6.44	3.12						
[9]	R	29	4.69	1.30	29	6.36	2.20						
	L		5.38	1.70		7.32	2.20						

Note: Italic = calculated for the present review using raw data or pooled means and SD.

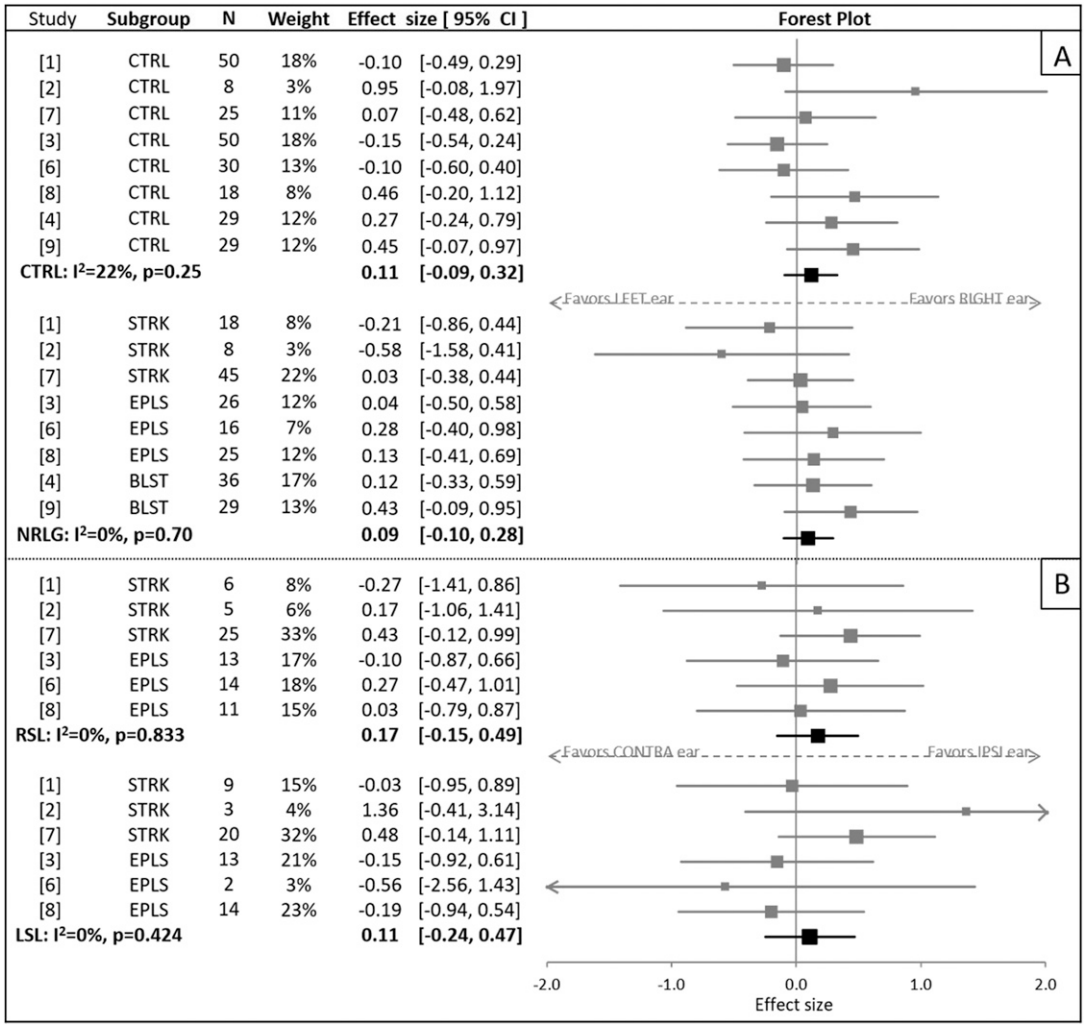

Figure 2. Comparison between RE and LE performance according to group (A) and between ipsilateral and contralateral ear's performance according to side of lesion (B). *From study [1], only participants with one-sided lesion were included in the analysis.

Only six studies included in this review reported on side of lesion and the difference in ipsilateral and contralateral ear performance (Figure 2B). Although data for NRLG participants with RSL and participants with LSL were deemed homogenous ($Q_{[11]} = 7.11$, $p = 0.790$; $I^2 = 0\%$), LSL ES were somewhat more disparate than RSL. The overall meta-analysis has shown a very small and nonsignificant ES for both groups pooled together ($d = 0.14$, 95% CI = −0.09, 0.39; $p = 0.236$), for RSL only ($d = 0.173$, 95% CI = −0.15, 0.50; $p = 0.295$) and for LSL only ($d = 0.11$, 95% CI = −0.25, 0.47; $p = 0.542$), with the three analyses slightly favoring the ear ipsilateral to the side of lesion (i.e., contralateral ear effect).

Difference between Groups: Has CTRL Better Performance than NRLG?

As observed in Table 2, the eight studies reporting on mean and SD presented homogenous data for both CTRL ($Q_{[15]} = 3.913$, $p = 0.998$; $I^2 = 0\%$) and NRLG ($Q_{[15]} = 2.204$, $p = 1.000$; $I^2 = 0\%$) groups. The CTRL pooled mean was 4.85 msec (95% CI = 4.35–5.35) and the NRLG pooled mean was 7.75 msec (95% CI = 6.46–9.04). All studies reported statistically significant larger GDT ($p < 0.05$) for the NRLG group compared with the CTRL group. In the RE, raw mean differences varied from 1.7 to 5.6 msec with large and significant ES ($0.87 \leq d \leq 2.50$). In the LE, raw mean differences varied from 1.9 to 3.9 msec with significant moderate to large ES ($0.78 \leq d \leq 2.68$). The subgroups' overall meta-analysis indicated that STRK and EPLS groups presented GDT 2.9 msec higher than CTRL groups, whereas BLST groups presented GDT 1.9 msec higher.

Because no significant difference between ear or side of lesion effects were seen on the previous analysis, data from both ears was pooled together using either the reported raw data or the pooled mean and SD (Higgins and Green, 2011). The ES for the mean difference between CTRL and NRLG groups were large and

significant for all studies and varied between 0.83 and 2.06, with better performance from CTRL groups (Figure 3). A nonsignificant but moderate degree of heterogeneity was observed among the studies. Such degree of heterogeneity was driven primarily by BLST studies that had lower overall ES ($d = 0.88$; $p < 0.001$) compared with both EPLS ($d = 1.54$; $p < 0.001$) and STRK studies ($d = 1.39$; $p < 0.001$). Overall ES for the mean difference between CTRL and NRLG groups, when considering all three subgroups, was largely significant ($d = 1.30$; $p < 0.001$) and also favored the CTRL group. Considering only the two more homogenous subgroups (i.e., STRK and EPLS), the overall ES increased to 1.47 ($p < 0.001$).

Is the GIN a Good Test to Discriminate between Neurological Patients and Control Participants?

Eight studies reported on data regarding number of patients and control participants with normal and abnormal performance to the GIN. Figure 4 shows similar cutoff points among all six studies and to what is proposed as norm [1], varying between 6 and 8.8 msec. Five studies based their choice of cutoff point on the mean for CTRL plus 2 SD [1, 3, 4, 8, and 9], one study used receiver operating characteristic analysis [6], and two studies used the published norm for the test [2 and 5]. Also from Figure 4, a considerably small FP rate (19/412 = 4.6%) and a somewhat significant FN rate (63/412 = 15%) were derived; the latter of which was probably driven by a majority of individuals in the NRLG group (~60%) performing normally on the GIN in both BLST studies. Without the BLST studies, overall FN rate decreases to 8.9% (26/291).

Among all studies, sensitivity rates varied from 40% to 94%, whereas specificity rates varied from 65% to 97% (Figure 4). The smallest sensitivity rates (<50%) were from BLST studies, of which most of the NRLG group had normal GIN performance, as previously mentioned. Including BLST studies, the overall sensitivity and specificity rates obtained using a bivariate model was 72% and 93%, respectively. Without BLST studies, the overall sensitivity rate raised to 80% and the overall specificity rate was the same (Figure 5).

Likelihood ratios help a clinician to reassess the odds of a given diagnosis in view of the patient's positive or negative test result (i.e., a positive result from a test with a large PLR suggests larger increase in the odds and a negative result from a test with a small NLR suggests larger decrease in the odds). Among all studies in this review, the PLR ranged from 2.1 to 28.1, whereas NLR ranged from 0.07 to 0.62 (Figure 6). The combined EPLS studies resulted in better likelihood ratios (PLR = 13.5; NLR = 0.10) than STRK (PLR = 8.3; NLR = 0.28) and BLST studies (PLR = 3.9; NLR = 0.57). Again, BLST studies presented the poorest rates. Despite considerable variability among studies regarding these indices, the overall PLR was 8.5 (95% CI = 3.9–18.5) and NLR was 0.28 (95% CI = 0.16–0.48). Without BLST studies, the overall PLR was 9.15 (95% CI = 3.35–25) and NLR was 0.22 (95% CI = 0.15–0.43).

The DOR is a measure of a test's effectiveness and should typically be >1. A DOR equal to 1.0 indicates that a given test is not a good predictor of the presence or absence of a given condition. Higher DOR are indicative of better test performance; therefore, DOR is better used to compare different tests' accuracy. This meta-analysis obtained DOR rates varying from 5 to 435 (Figure 6). The smallest DOR was from the study with the largest FP rate [5] followed by both BLST studies. The combined EPLS studies resulted in better DOR (106.7 [95% CI = 30.6–371.3]) than STRK (19.9 [95%

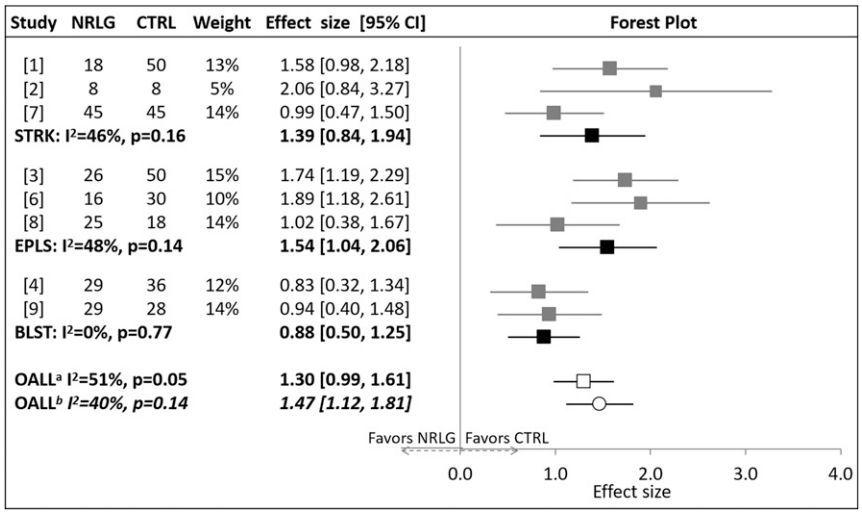

Figure 3. Comparison between CTRL and NRLG group performance for the GIN test, according to the study, subgroup, and overall studies. OALL = pooled studies; a = including BLST; b = without BLST studies.

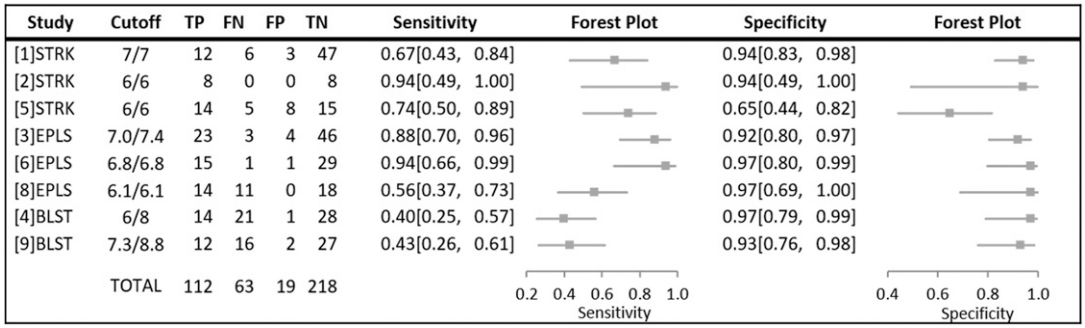

Figure 4. Summary of sensitivity and specificity rates obtained by the studies included in this review. Brackets = 95% CI. *Correction factor used.

CI = 3.2–123.2]) and BLST (12.7 [95% CI = 3.5–45.8]). Overall DOR was 30.5 (95% CI = 11.1–83.9) with BLST studies and 45.9 (95% CI = 11.7–179.6) without BLST studies.

Table 3 presents a summary of the overall rates obtained for a population with neuroauditory lesions (all studies combined), both with and without BLST studies. Despite the fact that the exclusion of BLST studies numerically improved all diagnostic measures obtained in this study, only the proportion of FN has been shown to be statistically significant and better (i.e., smaller).

DISCUSSION

It is widely known that neurological lesions might cause a variety of consequences related to AP, particularly to pattern and speech discrimination, localization, and binaural integration/separation (Musiek and Weihing, 2011). One important effect of unilateral neurological lesions concerns the laterality effect, that is, the effect a unilateral lesion has on the ear contra- or ipsilateral to the side of the lesion. In regard to temporal resolution, there are mixed findings in the literature about ear effects in gap detection tasks, with some studies showing ear differences for normal and neurological participants (Efron et al, 1985; Bamiou et al, 2006; Gallun et al, 2016) and several other studies not observing an asymmetry between ears' performances (Baker et al, 2008).

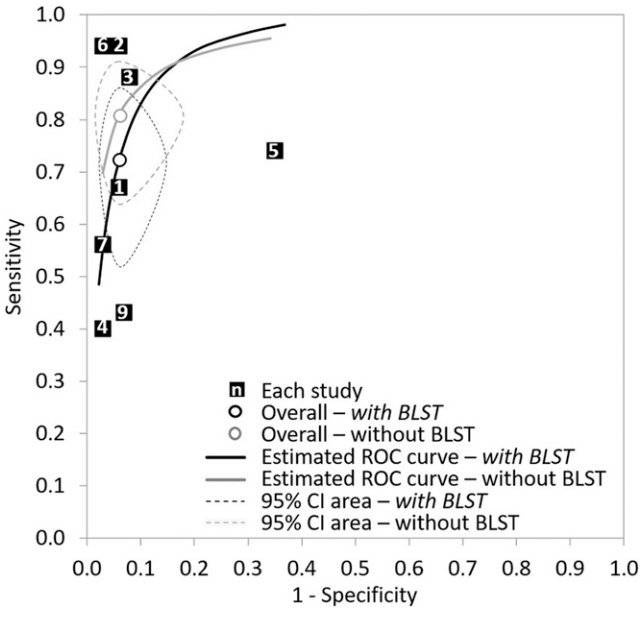

Figure 5. Summary receiver operating characteristic (ROC) curve calculated using a bivariate model.

In the present meta-analysis, both CTRL and NRLG groups showed only a small and nonsignificant ES for the difference between RE and LE, with a slightly better performance from the RE. In addition, from the studies that compared ear performance according to the side of lesion, only a small and nonsignificant ES with a slightly better performance to the ear ipsilateral to the lesion was shown. It is important to note that although some studies have shown moderate to large ES (~0.45 and above) for one or more of the four groups analyses (i.e., CTRL, NRLG, RSL, and LSL), none could be considered statistically significant (e.g., in the forest plot, the 95% CI bars touch/cross the Y axis, suggesting nonstatistically significant difference). In fact, studies [7] and [9] actually reported significant ear differences in the original articles, although neither one presented clear statistics confirming their statements. In addition, studies [2] and [6] consisted of very small sample sizes and, therefore, had little weight in the overall data, despite presenting considerable ESs. For instance, in the LSL group analysis, study [2] had a large ES (d = 1.36), favoring the ear ipsilateral to the lesion (i.e., contralateral effect) but had only 4% weight on the overall estimation of all four groups' analysis; and thus did not have a significant role on the overall estimation.

Therefore, based on the present review, differences regarding ear performance on the GIN should not be expected for adults with or without neurological pathologies, despite both groups showing a slight preference to the RE. Furthermore, one-sided neurological lesions

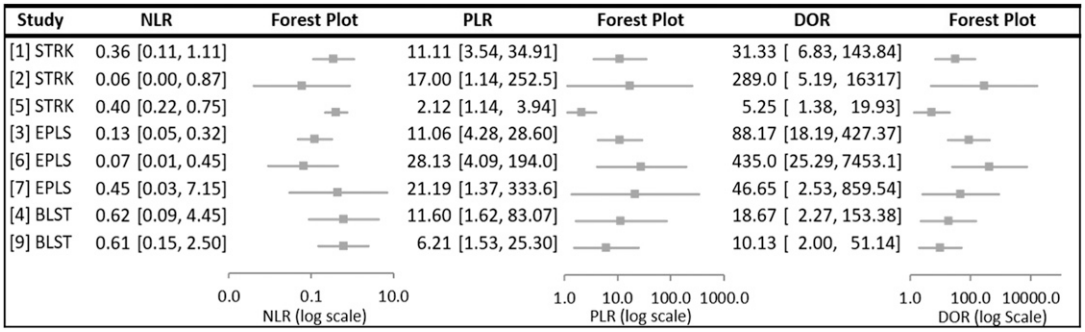

Figure 6. Summary of the ES for NLR, PLR, and DOR obtained for the studies included in this review. Brackets = 95% CI.

seemed to similarly affect GIN performance regardless of the ear being tested. Because gap detection tasks require synchronicity at multiple levels of the CANS, involving pathways both ipsilateral and contralateral to a lesion, laterality effects may be mitigated.

Regarding mean difference between groups with and without neurological conditions affecting the CANS, all the analyzed studies were homogenous in their results. The overall meta-analysis has shown that individuals with or at risk of neurological lesions to the CANS have poorer performance than individuals without known neurological conditions; demonstrating a large and significant overall ES ($d = 1.3$). For example, if one were to pick a single individual at random from each group, an individual from the CTRL group would have approximately an 82% chance of showing better performance compared with the NRLG group individual.

Despite the homogeneity among all studies, the ES was larger for EPLS studies, followed by STRK and then by BLST studies. A possible explanation for these differences lies within the variations associated with the origin of the individuals' neurological deficit. Temporal lobe epilepsy patients (i.e., the population observed in all three epilepsy studies included) present abnormal electrical discharges focused in the temporal lobe region that contains structures strongly associated with the CANS. Such abnormal discharges may lead to neuronal loss and localized lesions involving these specific structures and ultimately disrupt any associated functions. On the other hand, stroke patients present more diffuse and variable lesions that might involve other regions and functions of the brain. This could have led to either a larger variability in terms of performance, or to a lesser degree influence of the lesion

Table 3. Summary of the Diagnostic Measures Investigated in the Present Study with the Values Obtained for All Studies Combined, Including and Excluding the Blast Studies

		Observed in the Present Review		
Index	Definition	With BLST	Without BLST	*p* Value
TP	NRLG individuals presenting abnormal GIN	112	86	0.492
FN	NRLG individuals presenting normal GIN	63	26	0.012*
TN	CTRL individuals presenting normal GIN	19	16	0.589
FP	CTRL individuals presenting abnormal GIN	218	163	0.415
Sensitivity	Proportion of TP among all NRLG; indicates the odds of an NRLG individual presenting an abnormal GIN	72% (53–85%)	80% (64–90%)	0.127
Specificity	Proportion of TN among all CTRL; indicates the odds of a CTRL individual presenting a normal GIN	93% (86–97%)	93% (82–97%)	1.000
Positive likelihood ratio	Ratio between the proportion of TP among NRLG, and the proportion of FP among CTRL; indicates how much an abnormal GIN would increase the odds of having a neurological condition	8.5 (3.9–18.5)	9.15 (3.35–25)	0.908
Negative likelihood ratio	Ratio between the proportion of FN among NRLG, and the proportion of TP among CTRL; indicates how much a normal GIN would decrease the odds of having a neurological condition	0.28 (0.16–0.48)	0.22 (0.15–0.43)	0.633
DOR	Ratio between how much an abnormal GIN increases the odds of being NRLG and how much a normal GIN decreases the odds of being NRLG; a single measure of a test's effectiveness.	30.5 (11.1–83.9)	45.9 (11.7–179.6)	0.638

Brackets = 95% CI.

*$p < 0.05$.

in some stroke individuals, compared with EPLS individuals.

The smaller ES from BLST studies, however, can be explained by the fact that the NRLG group in these studies contained individuals who had been exposed to blasts despite NO confirmed neurological lesions. In fact, the largest part of the NRLG group in both BLST studies (~60%) had normal performance to the GIN test, despite having an average poorer performance compared with CTRL. Because of this, the results prompted the authors to question including these two studies in the present review. However, because both studies have shown large and significant ES ($d \geq 0.8$, $p < 0.05$), it is evident that being exposed to a blast explosion, regardless of TBI diagnosis, may lead to poorer temporal resolution performance, even if it is a lesser degree compared with the other two neurological conditions. It was ultimately decided that these data should not be dismissed but that its influence to the overall data should be investigated in more detail.

These differences in the particularities of each condition might also be the cause of the lack of homogeneity in terms of sensitivity, likelihood ratios, and DOR, among the included studies. In opposition, it is noteworthy that the GIN test specificity rate was very homogenous with great consistency among non-neurological individuals, despite the included studies being from different countries with different languages and cultural backgrounds. Only one study diverged from the others regarding specificity. Study [5] had a large proportion of FP, which led to a significantly lower specificity rate. This can be explained by the age of their participant group and the cutoff scores they used. In this study, nearly half of the 23 CTRL individuals were older than 60 years, an age range that has demonstrated higher GDT compared with younger adults (Murphy et al, personal communication). It may be argued that if the authors of study [5] had chosen to use cutoff scores based on their own CTRL group average performance, the specificity rate would have been similar to the other studies. Because we do not have access to the raw data for this study, such hypotheses could not be reliably tested.

The set of measures of diagnostic accuracy calculated in this analysis returned very good rates, with small but nonsignificant improvement when excluding BLST studies. It was shown that dysfunctions related to neurological lesions of the CANS can be suggested by an abnormal GIN test performance with an overall sensitivity rate of 72% and specificity rate of 93% (without BLST = 80% and 93%, respectively). The high PLR and low NLR also demonstrate that an abnormal GIN performance would significantly increase the suggestion of a neurological lesion/dysfunction related to the CANS, and a normal GIN performance would significantly decrease such a suggestion. Finally, the relatively large DOR obtained for the overall analysis (with BLST = 30.5; without BLST = 45.9) not only indicates an accurate test but also supports the previous findings demonstrating that the GIN is more efficient in differentiating patients with epilepsy (106.7) from neurologically normal individuals, compared with patients who have had a stroke (19.9) or even blast-exposed patients (12.7).

The good accuracy rates in identifying individuals with neuroauditory lesions, along with the overall consistent performance of normal controls, showcase the GIN test as a powerful clinical tool that can be used to investigate temporal resolution dysfunction and be used reliably across languages and cultures. Clinicians should be aware of the diagnostic value and utility the GIN test provides, particularly when considering an audiological assessment battery for individuals with or at risk of neurological lesions. Once a CANS dysfunction is identified, specific intervention targeting AP might help these individuals' communication and improve their quality of life.

CONCLUSION

The GIN is, thus, a clinically effective measure that provides insight into the CANS integrity and may aid in clinical diagnosis by distinguishing between populations who are and who are not at risk of having neurological damage affecting the CANS.

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