Language Bilaterality:
A Systematic Review of Bilateral Language Dominance in Wada Studies

By

Julie Beals

Thesis

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

In

Speech-Language Pathology

April 29th, 2021

Nashville, Tennessee

Approved:	Date:
Stephen Wilson, PhD, via email	May 29th, 2021
Michael de Riesthal, PhD, CCC-SLP, via email	June 1st, 2021
Monica Jacobs, PsyD, ABPP, via email	May 29th, 2021

ABSTRACT

Objective: To determine and graphically represent the ways that language bilaterality is defined in Wada studies, and to estimate the prevalence of language bilaterality according to those definitions.

Methods: A systematic analysis of 33 Wada studies was conducted. All Wada studies were published in English, did not use children as participants, were primarily or substantially concerned with language laterality, and included at least 100 participants who underwent the Wada procedure. Definitions for language laterality categories and language laterality distributions were collected from each article. This information was used to generate lateralization matrices. In the lateralization matrices, the vertical axis represents the independent functioning of the right brain hemisphere and the horizontal axis represents the independent functioning of the left brain hemisphere. The matrices provide a visual representation of the behavior that the researchers attributed to different categories, and include the number of patients assigned to each category.

Results: The definitions of language bilaterality from the 33 studies fell into four broad categories and were represented graphically with 26 matrices. There were seven articles for which a matrix could not be constructed. The prevalence of language bilaterality was estimated as 9.8% with an *SD* of 4.3%, the prevalence of left-hemisphere dominance was estimated as 78.0% with an *SD* of 6.6%, and the prevalence of right-hemisphere dominance was estimated as 8.5% with an *SD* of 4.4%. The mean proportions of patients with bilaterality (9.8%) and patients with right-hemisphere lateralization (8.5%) were similar, so the articles were organized into the following groups: (1) right-hemisphere lateralization proportion > bilaterality proportion; (2) bilaterality proportion > right-hemisphere lateralization proportion; and (3) right-hemisphere proportion within 0.2% of bilaterality proportion. The set of matrices in each group were then examined to investigate whether there is a relationship between the way these two proportions vary with respect to one another and the articles' definitions of the categories. No pattern was found among these sets of matrices that could account for the variance.

Conclusion: This collection of Wada studies suggests that the prevalence of language bilaterality is approximately 9.8% in the populations they investigated. While the analysis of the matrices generated in this study did not yield a clear pattern in matrix configuration and the variance of right-hemisphere lateralization and bilaterality with respect to one another, laterality matrices may still be useful for future research, as they provide a means of graphically comparing disparate definitions of laterality categories.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

Many thanks to my thesis advisor, Stephen Wilson, Ph.D., and Sarah Schneck, M.S., my graduate student thesis advisor.

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Laterality as a term

The term “language laterality” refers to the location of the neural substrates that underlie an individual’s language abilities (Wegrzyn et al., 2019). Specifically, it refers to which brain hemisphere those substrates occupy. For this reason, it is often called “hemispheric language dominance” (Keller et al., 2017). An individual can be said to have left hemispheric language dominance, meaning that all or the majority of their language abilities are represented in their left hemisphere, or right hemispheric language dominance, meaning that all or the majority of their language abilities are represented in their right hemisphere. The term “hemispheric language dominance” also carries with it the implication that the neural substrates for language may reside in both hemispheres, but be *dominantly* present in one or the other. The condition in which the neural substrates for language exist in both hemispheres is referred to as “bilateral language dominance,” or, as it will be referred to in this paper, “language bilaterality” (Möddel et al., 2009).

Left-lateralized majority

There is a long history of research indicating that, in most people, language is lateralized to the left hemisphere of the cerebral cortex. According to Moser et al. (2011), this concept has been supported by research findings since the early 19th century. However, the size of that left-hemisphere majority was not estimated until much later (Moser et al., 2011). In one of the most well-cited early Wada studies, Rasmussen and Milner (1977) reported that 96% of right-handed patients and 70% of left-handed patients demonstrated left-hemisphere dominance. Their study included 396 patients and provided the scientific world with insight into the trends of language lateralization. But there is reason to suspect that Rasmussen and Milner's proportions may not be representative of the typical population, as all of their patients had an epilepsy diagnosis. Patients with an early onset of epilepsy are at an increased risk for language reorganization (Tracy et al., 2009). This language reorganization may involve "a full shift of all language skills to the contralateral hemisphere," or possibly a shift of only a subset of language skills (Tracy et al., 2009). Thus, if this had been the case with any of Rasmussen and Milner's patients, their estimated prevalence of left-hemisphere language lateralization would not be true of the general, neurotypical population.

Cases of acute unilateral brain injury, such as stroke or trauma, also provide insight into the prevalence of left-hemisphere language lateralization (Moser et al, 2011). If an individual has language localized in their left hemisphere and experiences a unilateral left hemisphere stroke or trauma and then presents with aphasia (i.e., impairment of language abilities), it follows that their language abilities were lateralized on the left, because the left hemisphere was the only hemisphere that sustained damage. Moser et al. (2011) conducted an analysis of several large-scale studies, investigating the frequency with which unilateral left-hemisphere stroke results in aphasia. In other words, they studied stroke patients to estimate the prevalence of left-hemisphere lateralization in the general population. When they averaged the proportions of left-hemisphere lateralization in those studies, they found that it was 90% (Moser et al., 2011). Other studies report that this 90% estimate is only accurate for right-handed individuals, and that it decreases in left-handed individuals (Keller et al., 2017).

As a result of this clear left-hemisphere lateralization majority, the term "atypical language laterality" was coined. This term refers to language laterality that is either right-hemisphere lateralized or bilateral, and appears in several of the articles included in this study (Janszky et al., 2003; Woermann et al., 2003; Akanuma et al., 2003; Miller et al., 2005; Isaacs et al., 2006; Kovac et al., 2010).

Handedness

As implied above, handedness is known to have a relationship with language lateralization. It's well-established that left-handed individuals more frequently have atypical language lateralization than right-handed individuals (Knecht et al., 2000; Drane et al., 2012). Isaacs et al. (2006) found that "the incidence of atypical language dominance increased linearly with the degree of left-handedness." They assessed handedness using the Edinburgh Handedness Inventory and found that incidence of atypical laterality was 9% for what they describe as "strong" right-handers, 46% for ambidextrous individuals, and 69% for "strong" left-handers. Thus, they demonstrated a strong positive correlation between left-handedness and atypical language laterality. The results of Kamada et al.'s (2007) study—in which 6.3% of right-handed, 33% of ambidextrous, and 50% of left-handed patients demonstrated atypical language laterality—corroborate this trend.

Early brain injury

Early brain injury is associated with language laterality because it is believed to cause language reorganization in some cases (Rathore et al., 2009). According to Tracy et al. (2009) and Rathore et al. (2009), there is a wealth of evidence supporting the idea that language laterality is established by age six. If an adult is known to have sustained a brain injury prior to age six, it is considered more likely that their current language laterality differs from that of their childhood, before the injury. This age of language lateralization establishment is especially important to note, because the Wada procedure is most commonly administered to epilepsy patients, and epilepsy can result from brain lesions (Lucke-Wold et al., 2015). Thus, there is a relationship between the age at which epileptic seizures begin and language lateralization. For example, Tracy et al. (2009) found that the onset of dominant temporal lobe seizures prior to age six leads to a more atypical language laterality, especially for the tasks of naming and reading. Findings such as this highlight the importance of accounting for age of seizure onset, and any early brain injuries, in Wada studies. If it is not accounted for, the estimated prevalence of atypical language laterality will likely be inflated.

Language bilaterality

Researchers vary in how they define language bilaterality. Some researchers, such as Loring et al. (1990), have posited that language bilaterality includes cases in which the majority of a patient's language ability is represented by one hemisphere and a small fraction of their language ability is represented by the other hemisphere. In terms of Wada studies, this would be denoted by severe language deficits when one brain hemisphere is anesthetized and mild language deficits when the other is anesthetized. Other researchers, such as Helmstaedter et al. (1997), have posited that such cases should be categorized as dominance of the hemisphere that demonstrates the majority of language ability. Additionally, there are some researchers, such as Cunningham et al. (2008) and Keller et al. (2018), who have demonstrated a belief that an individual only has true language bilaterality if their capacity for language is equally represented in each of their hemispheres.

Cases in which language bilaterality is defined as equal representation of language in each hemisphere can be further divided into two groups: (1) Those in which each hemisphere succeeds at the same *proportion* of language tasks with respect to the total set of tasks (e.g., each hemisphere is able to successfully complete 2 out of 5 tasks); and (2) Those in which each hemisphere succeeds at the same *specific* language tasks with respect to the total set of tasks (e.g., each hemisphere is able to successfully complete tasks #1 and #4 out of 5 tasks, and none of the others). Both of these groups could be considered to denote a form of symmetry in language ability.

This variance in how researchers define language bilaterality makes it difficult to estimate the prevalence of language bilaterality. Two researchers could study the same set of patients, and use the same methodology (e.g., Wada, fMRI, electrocorticography) to determine the laterality of those patients, but produce quite disparate results simply because they had different criteria for classifying a patient as bilateral. For example, one researcher might find that 13% of their patients has language bilaterality, and the other might find that 4% of their patients has language bilaterality (e.g., see Loring et al., 1990 and Kurthen et al., 1992, respectively). Further, this variance makes it challenging to assess the concordance between Wada studies—or, indeed, the concordance between Wada studies and those of other methodologies that investigate language laterality. This is hindering efforts to replace Wada studies with fMRI studies, which is a current movement within the scientific community.

Role of Wada in assessing language laterality

The Wada procedure is currently considered the gold standard in assessing language laterality (Keller et al. 2018). However, Hirata et al., 2010 points out that the Wada procedure is “an invasive test that involves the risks associated with cerebral angiography.” They explain that “complication rates of 1.2–17.0% have been reported, as have 0.3–6.9% rates of neurological complications, including transient ischemic attach (0.3–2.1%), cerebral infarction (0–1.0%), hematoma at the puncture site (0.4–4.2%), arterial dissection (0.07–0.4%), and allergic reaction (0.03–0.1%).” Relatedly, Branch et al. (1964), one of the earliest Wada studies examining language laterality and the earliest Wada study included in this review, cautions the scientific community that Wada “should, therefore, not be used indiscriminately, but only when an accurate knowledge of the mode of representation of speech would contribute materially to the management of the patient.” Thus, if scientists wish to study language laterality in individuals who do not have epilepsy or another neurological impairment for which the Wada procedure is medically indicated, they must instate another methodology as the gold standard.

History of Wada procedure

The Wada procedure originated with Dr. Juhn Wada, a Japanese-Canadian neurologist and epileptologist, who developed it in the 1940s while working as a medical resident in Japan (University of British Columbia, 2019). The first paper on the Wada procedure was published in 1949, and it was in Japanese (McElligott, 2011; Wada, 1949). Dr. Juhn Wada later introduced his procedure to English speakers while completing a fellowship at the Montreal Neurological Institute. The protocol he taught at the Montreal Neurological Institute is referred to as “the Montreal protocol,” is still widely used.

The Wada procedure was originally developed to assess only language laterality, and became “a routine component of the preoperative evaluation for epilepsy surgery” in the 1950s (Loring and Meador, 2019). It is critical that a patient's medical team ascertain the location of their neural substrates for language, because otherwise those substrates may be harmed or excised during surgery. Today, the Wada procedure remains a part of presurgical work-up for epilepsy patients, but it is now commonly used to assess both language and memory laterality. The hippocampi, which are heavily involved in memory function, lie in the medial temporal lobe of each brain hemisphere. Thus, when a patient has temporal lobe epilepsy, a surgical resection carries the risk of compromising memory function. The hippocampi's role in memory formation was not well-understood in the 1950s, and that is why memory lateralization was not yet established as part of the presurgical work-up (Loring and Meador, 2019).

Additionally, the Wada procedure is now occasionally administered to patients with disorders other than epilepsy. For example, Miller et al. (2005) states that patients with arteriovenous malformations or brain tumors have also undergone the procedure. There are several studies in this review that included patients with arteriovenous malformations or brain tumors (e.g., Branch et al., 1964 and Kurthen et al., 1994).

Wada procedure

The procedure begins with an angiogram, which is a radiological image of the brain's blood vessels (Keller et al, 2018). A catheter is inserted into the patient's femoral artery, typically in the groin area, and guided into the patient's internal carotid artery. A contrast medium is then injected into the catheter (Rasmussen & Milner, 1977). This allows the medical team to preview the course that the anesthetic will take through the patient's vascular system. The purpose in doing this is to verify that only one brain hemisphere will be anesthetized, because there are cases in which both hemispheres become anesthetized. This is referred to as "cross-filling" (Fedio et al., 1997), "double-filling" (Ishikawa et al., 2017), or "crossflow" (Janecek et al., 2013). It arises from some form of anatomical irregularity in the patient's vascular system. Patients who demonstrate cross-filling are considered to be non-diagnostic for the purposes of assessment, because even if the patient were able to participate in the administered tasks, the anesthetization of both hemispheres renders it impossible to determine which hemisphere is supporting the behavior—or to what *degree* each hemisphere is supporting the behavior.

If it is found that the patient does not have cross-filling, they are given a “dry run” of the language tasks to be administered during the procedure (Rasmussen & Milner, 1977). This confirms that they understand the language tasks at baseline. Some medical teams conduct the dry run on a date prior to the procedure. The most common language tasks administered in the studies included in this review are as follows: counting backwards from 100; comprehension of spoken commands and questions; confrontation naming; sentence repetition; and reading simple and/or complex sentences. Almost invariably, the task of counting backwards from 100 is the first administered.

When the medical team is preparing to inject the anesthetic, they ask the patient to hold both of their arms up, in a mummy-like position. This is done because the anesthetic will travel to the hemisphere that’s contralateral to the injected leg. Accordingly, the anesthetic will also cause hemiparesis on the contralateral side of the patient’s body (Drane et al., 2012). This will cause their contralateral arm to drop (Ishikawa et al., 2017). The dropping of the contralateral arm is one of the markers that the anesthetic has taken effect. The patient is also connected to EEG and should demonstrate delta slowing (i.e., slowing of brain waves) when the anesthetic has taken effect (Janecek et al., 2013). Once anesthetized, the brain hemisphere should be nonfunctional. This causes “the hemisphere with language representation to be revealed when language deficits appear during an injection” (Drane et al., 2012).

The drugs employed for the Wada procedure include the following: amobarbital (i.e., sodium amytal), methohexital, pentobarbital, etomidate, and propofol (Loring & Meador, 2019; Kovac et al., 2010; Passarelli et al., 2014). The time of effect varies for each drug. The anesthetization typically lasts for 3–15 minutes. The bolus, which is the amount of the drug pushed, also varies. The range of bolus size among the studies that were included in this review varied from 100 to 250 milligrams (e.g., Loring et al., 1990). There are instances in which a patient becomes too obtunded from the drug to perform any language tasks (Janecek et al., 2013), in which case they are considered nondiagnostic for the purposes of assessment. However, many of the studies in this review distinguish obtundation from prolonged speech arrest. Obtundation is the condition in which the patient is not sufficiently alert; prolonged speech arrest is the condition in which the patient is sufficiently alert but not producing speech when prompted (Möddel et al., 2009).

The Wada procedure is typically administered bilaterally (Rasmussen & Milner, 1977). The whole process, from the angiogram to the administration of language tasks, is completed on the patient's one side, and then the medical team will repeat the process on the patient's other side once the effects of the anesthetic have worn off. The earliest study in this review, Branch et al. (1964), stated that it is ideal to conduct each procedure on separate days. However, many researchers only wait approximately 30 minutes before administering the second procedure (e.g., Keller et al., 2013).

Categorizing patients based on Wada results

Once the Wada procedure has been administered bilaterally, the researchers or medical team must determine the laterality category to which the patient belongs. If a patient cannot use language at all when their left hemisphere is anesthetized and has no deficits when their right hemisphere is anesthetized, the patient clearly has left-hemisphere lateralization. If a patient cannot use language at all when their right hemisphere is anesthetized and has no deficits when their left hemisphere is anesthetized, the patient clearly has right-hemisphere lateralization. However, performance on language tasks is not always this cleanly divided. Patients are often be able to complete some language tasks correctly during each anesthetization. That is why, in addition to left-hemisphere lateralization and right-hemisphere lateralization, there is a category of bilaterality, and occasionally the following categories: incomplete right-hemisphere lateralization (Helmstaedter et al., 1997); incomplete left-hemisphere lateralization (Kurthen et al., 1992); bilateral dependent lateralization and bilateral independent lateralization (Möddel et al., 2009); and partial reliance (Moser et al., 2011).

It is also sometimes the case that a patient will appear to have expressive language abilities supported by one brain hemisphere and receptive language abilities supported by the other. This is referred to as "dissociative lateralization" and is extremely rare. Moser et al. (2011) conducted a careful review of focal lesion studies and found a total of less than 20 individual cases in which there was dissociative lateralization.

Research questions

My research questions were as follows:

1) How is language bilaterality defined in Wada studies, and how can those definitions be represented graphically?
2) What is the prevalence of language bilaterality according to those definitions?

Significance of research questions

These research questions were worth investigating for the following reasons:

1) The nature of the neural substrates underlying language are not completely understood. The question of why they may be located in both brain hemispheres and the degree to which they may be located in both brain hemispheres is unanswered.
2) The nature and prevalence of language bilaterality, if determined, could potentially inform procedures for epilepsy surgery. Consider the following scenario: Two patients are judged to have language bilaterality, but one patient demonstrates mild language deficits for both Wada injections, and the other patient demonstrates one set of language abilities for one Wada injection and another set for the other injection. The first patient might undergo surgery and experience only mild or no language impairment afterward. The second patient might undergo surgery and loose an entire set of language abilities (e.g., their receptive language abilities). If language bilaterality were better understood, medical teams could take such information into account when considering and communicating about a patient's eligibility for surgery.

3) Definitions of language bilaterality must be better understood in order to establish concordance between Wada studies and fMRI studies that investigate language laterality. Concordance needs to be established in order for fMRI to replace Wada as the gold standard method for assessing language laterality. Further, is desirable for fMRI to replace Wada, because fMRI is not invasive (i.e., it is not a surgical procedure), it is less expensive, it can be repeated without risk to the patient, and it allows for intrahemispheric localization as well as interhemispheric localization. When there is discordance between the language bilaterality proportions that are reported in fMRI and Wada studies, disparate definitions of language bilaterality may be the cause.
4) There is potential for knowledge about the prevalence of language bilaterality to affect the practice of speech-language pathologists. Currently, it is common practice for speech-language pathologists to not screen for language impairment unless it is suspected, and it is typically suspected if a patient has left hemisphere damage, or is left-handed and has right hemisphere damage. If it were accepted that language bilaterality is more common than it is currently believed to be, this practice would likely change. It could result in speech-language pathologists screening for aphasia in a wider variety of cases.

CHAPTER 2

METHODS

We reviewed studies that had used the Wada procedure to investigate language laterality. We collected the studies from PubMed on April 3rd, 2020, using the following phrase:

> (("wada test" OR "wada test" OR "wada procedure" OR "wada procedures" OR "wada testing") OR ((amobarbital OR amytal) AND (speech OR language OR hemispheric OR hemisphere OR dominance OR intracarotid)))

This produced 1,018 results. We culled from the results using the following additional criteria:

1) The study was published in English
2) The participants were not children
3) The study was primarily or substantially concerned with language laterality as assessed by the Wada procedure, including studies that relate lateralization per the Wada procedure to other measures of language lateralization
4) $n \geq 100$ received Wada; some participants within that *n* may have been nondiagnostic.

This narrowed the results to 33 studies. The rationale behind not including studies of children was that language laterality may not be established in all children. The rationale behind requiring that each study have at least 100 participants was that a larger *n* would contribute to a more accurate estimation of language bilaterality prevalence. A study did not necessarily have to report laterality for 100 participants; it simply had to attempt to administer Wada to at least 100 participants. Thus, if a study began with 100 participants and it was later determined that some of those participants were non-diagnostic (e.g., due to cross-filling during the angiogram or obtundation after anesthetization), the study could still be included.

Once we collected those 33 studies, we created a list of data extraction items to apply to each one. Those items were as follows:

1) What is the article title and who are the authors?
2) What is the publication date?
3) What is the journal?
4) What is *n*?
5) Is handedness reported for participants? If so, how many of the participants were right-handed, left-handed, or otherwise?
6) Is age reported for participants? If so, how old were the participants (e.g., mean, range, etc.)?
7) Is sex reported for participants? If so, how many were female and how many were male?
8) If participants qualified for the study based on the presence of a specific medical condition (e.g., temporal lobe epilepsy), what was that medical condition? Were there any participants who did not have that medical condition?
9) If participants qualified for the study based on the presence of a specific medical condition (e.g., temporal lobe epilepsy), what was the age of onset?
10) Which brain region(s) were the locus of pathology or the origin of epileptogenic activity?
11) What language did the participants speak?
12) Were any participants deemed nondiagnostic? If so, how many, and why?
13) Were the Wada tests unilateral or bilateral?
14) What anesthetic was used to administer the Wada procedure (e.g., amobarbital)?
15) What language tests were administered during the Wada procedure?
16) What was the timing of language testing relative to the injection and relative to the evidence for return of function?

17) Did the researchers make any comments about cross-filling or incomplete anesthetization?
18) What conditions needed to be present in order for the authors to conclude that a patient had left-hemisphere, right-hemisphere, or bilateral language dominance?
19) Are there any observations made about the nature of disruption or sparing of language in the left-hemisphere, right-hemisphere, or bilateral language dominance categories?
20) Were other methods for determining laterality included? If so, what were they?
21) What is the reported distribution(s)?

These items can be divided into the categories of publication (1–3), participant (4–12), Wada procedure (13–17), and laterality determination (18–21). The “distribution” refers to how many patients fell into each of the study’s language laterality categories. Only a subset of these items was ultimately used to address our research questions. This subset is listed for each individual article in the Appendix.

To graphically represent these studies’ definitions of bilaterality, we designed a laterality matrix template (Figure 1). In the template, the vertical axis represents the independent functioning of the right brain hemisphere, and the horizontal axis represents the independent functioning of the left brain hemisphere. The degree of functioning is delineated with the following descriptions of language ability: global aphasia; severe deficits; moderate deficits; mild deficits; and no deficits.

	When only left hemisphere is "on"				
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					
Severe					
Moderate					
Mild					
No deficits					

Figure 1. Lateralization matrix template

The template's cells were then populated for each study, using the study's definitions of laterality categories. A color code was used. The color red represents right-hemisphere lateralization; blue represents bilaterality; green represents left-hemisphere lateralization; and purple (the combination of red and blue) represents atypical lateralization. In studies for which there were incomplete left-hemisphere and incomplete right-hemisphere lateralization categories, incomplete left-hemisphere lateralization was represented with light green and incomplete right-hemisphere lateralization was represented with light red. In studies with additional categories, a new color was assigned (Figure 2). The distribution figures were keyed into each area of colored cells, indicating how many patients were designated as belonging to each category.

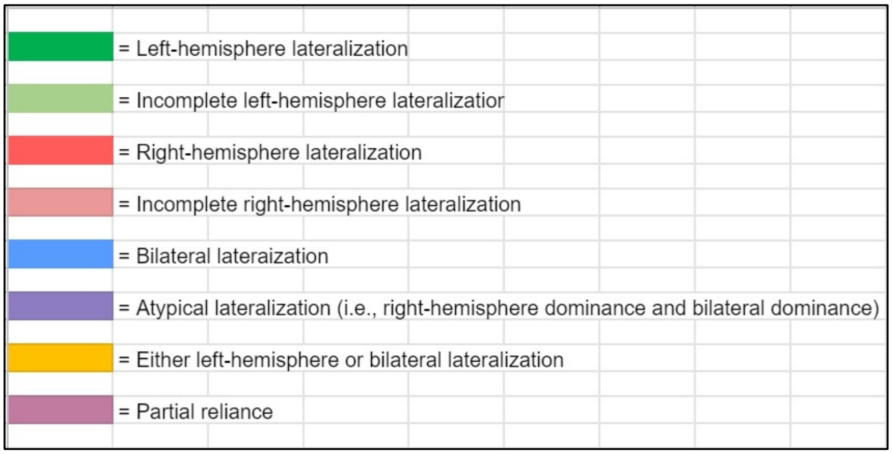


Figure 2. Matrix color code

To populate a matrix, the definitions for each lateralization category were mapped onto the terms used in the matrix (i.e., global aphasia, severe deficits, etc.). For some studies, this was simple, because the study used the same terms that we used to describe a patient's degree of language impairment. For other studies, this was less simple, because their terms were quite disparate from those of our matrix. Both the laterality category definitions and the rationale for each matrix configuration is listed in the Appendix.

To estimate the prevalence of language bilaterality, the proportion of patients in each lateralization category was calculated for each study. In calculating the proportions, the number of patients who were categorized, rather than the study's overall *n*, was used as the denominator. The reason for this is that the study's *n* includes the nondiagnostic patients. Theoretically, all of those nondiagnostic patients have a specific language lateralization, but it could not be determined via the Wada procedure. If those nondiagnostic patients were included in the denominator, the resultant proportions would be inaccurate. For example, if a study's *n* was 100, and 20 of the patients were nondiagnostic, 80 patients would be categorized. If 40 of those 80 patients demonstrated left-hemisphere lateralization, it would be inaccurate to use *n* as the denominator and claim that 40% of the study's patients were left-hemisphere lateralized. It might be that the 20 nondiagnostic patients were *also* left-hemisphere lateralized, and in that scenario, the true proportion of left-hemisphere patients would be 60%—a much larger proportion. Therefore, to account for the unknown and be as accurate as possible, the proportion of left-hemisphere lateralized patients would have been calculated as 50%.

CHAPTER 3

RESULTS

Definitions of language bilaterality

The systems that researchers used to organize patients into language laterality categories fit into the following groups: (1) Utilization of a lateralization index (e.g., Kurthen et al., 1994); (2) Reliance on duration of speech arrest (e.g., Benbadis et al., 1995); (3) Utilization of a scoring system with which points are assigned during language tasks (Risse et al., 1997); and (4) Utilization of purely qualitative descriptions (e.g., Branch et al., 1964). The systems are described for each individual article in the Appendix.

Regarding the matrices, out of the 33 articles, there were seven for which a matrix could not be built. Out of those seven, three were excluded from the study altogether (i.e., their distribution data was not included in the quantitative analysis). We decided that the articles for which a matrix could not be built should not be categorically excluded from the study, because one of the peripheral aims of this study was to determine whether there is consistency across articles in the proportion of patients with language bilaterality. Including the maximum number of studies that met the original inclusion criteria best serves that aim. The explanations for why a matrix could not be constructed and/or why an article's distribution data was not included in the quantitative analysis is detailed in Table 1. In the table, each article's number corresponds with its position in Appendix, which is ordered chronologically, according to publication date.

Table 1. Articles for which a matrix could not be constructed

Article	Reason matrix could not be constructed	Distribution included in study?
3. Woods et al. (1988)	Researchers do not define their laterality categories.	Yes
9. Kurthen et al. (1997)	Researchers do not list a true distribution; they only list the average lateralization index score for the men and the women.	No
12. Loring et al. (1999)	Researchers do not define their laterality categories.	Yes
13. Janszky et al. (2003)	Researchers do not define their laterality categories.	Yes
21. Kamada et al. (2007)	While researchers list *n* as 117, Wada is only administered to 97 patients, with 6 of those 97 being nondiagnostic. Thus, *n* is not actually ≥ 100.	No
27. Uijl et al. (2009)	Researchers do not define their laterality categories.	Yes
28. Hirata et al. (2010)	While researchers list *n* as 123, Wada is only administered to 77 patients, with their nondiagnostic patients included in that 77 count.	No

An important distinction should be made with regard to Kamada et al. (2007). While there are other studies (e.g., Loring et al., 1990) that list a subset of patients as "excluded," which seems to suggest that their *n* may not have been greater or equal to 100, those studies include their nondiagnostic patients in that "excluded" group. The patients for whom Wada was attempted but not fully administered are in the "excluded" group. This is not the case for Kamada et al. (2007). Kamada et al. (2007) had nondiagnostic patients, but those patients were included in the count of 97 patients who received the Wada procedure. They do not account for the 20 patients with whom the Wada procedure was not even attempted. Thus, their true *n* is 97; not 117. Moreover, the reason that Kamada et al. (2007) was not eliminated from the study altogether, making the total article count 32, was that the article technically *does* meet this study's inclusion criteria, as it is written and presented. It was only at the point of data analysis that Kamada et al. (2007) was found to be ineligible for inclusion.

Thus, there were a total of 26 articles for which matrices could be built. Of those 26 articles, there were six for which multiple distributions were reported and for which multiple matrices could be built (Table 2).

Table 2. Articles for which multiple matrices were generated

Article	Reason for multiple matrices	Number of matrices
2. Rasmussen and Milner (1977)	The distributions reported are for separate subgroups of *n.* The first is the subgroup of patients without evidence of early left-hemisphere injury; the second is the subgroup with evidence of early left-hemisphere injury.	2
1. Loring et al. (1990)	There are two separate classification systems used in the study: "exclusive language representation" and "forced relative dominance." A distribution is reported for each classification system.	2
7. Kurthen et al. (1994)	An overall distribution is provided, in addition to a distribution comprises of subcategories of bilaterality.	2
15. Miller et al. (2003)	The distributions reported are for total *n* and two separate subgroups of *n*. The first subgroup is of patients with normal neurological histories; the second subgroup is of patients without normal neurological histories or who did not have infarct leading to epilepsy after age 15.	3
26. Tracy et al. (2009)	Distributions are reported for each language domain: reading, naming, comprehension, repetition, and speech.	5

30. Moser et al. (2011)	Distributions are reported for the intersection of two categories: expressive language abilities vs. receptive language abilities, and right hemisphere pathology vs. left hemisphere pathology.	4

Language bilaterality prevalence

The major challenge in estimating the prevalence of language bilaterality is that, as explained previously, six of the articles listed multiple laterality distributions. Those multiple distributions could not be entered into the data analysis, because in some cases, that would mean counting individual patients twice. Also, in studies such as Loring et al. (1990), for which there were multiple classification systems used, the researchers do not express a preference for one classification system over another. It would be unjustified to select one of the systems and exclude its distribution from the data analysis, in favor of the other.

In the case of Rasmussen and Milner (1977), only the distribution for which patients did not have clinical/radiological evidence of early left-hemisphere brain injury was used for data analysis. The rationale was that doing so would contribute to a more accurate estimation of language bilaterality in the general population. Also, this distribution consisted of 262 patients, so it did not violate any of the initial inclusion criterion. For Kurthen et al. (1994), a general distribution for *n* is reported, and the second reported distribution is simply a detailed breakdown of the bilateral patients, based on behavior. Thus, it was sensible to use the general distribution for data analysis. Similarly, for Miller et al. (2003), a general distribution for *n* is reported, which includes the patients who were listed in the other two distributions, so we used that general distribution for analysis.

For the other three articles listed in Table 2, the proportions for each laterality category were averaged across the reported distributions. The full list of proportions for each article, with the means and standard deviations in each lateralization category, can be viewed in Table 3. There were 30 articles in total that were included in the data analysis.

Table 3. Proportions of each laterality category with respect to each article's *n*. Grey rows denote articles for which a matrix could not be constructed.

	Left	Incomplete Left	Left and Bilateral	Right	Incomplete Right	Bilateral	Bilateral Dependent	Bilateral Independent	Partial Reliance	Atypical	Pattern	Overall Left (Left + Incomplete Left)
1	64.7			26.9		8.4					R > B	64.7
2	84			9.2		6.9					R > B	84
3	83.7			7.7		8.7					w/in 2%	83.7
4	83			3.85		13.15					B > R	83
5	71.6	15.5		8.1		4.7					R > B	87.1
6	72.2	16		7.6		4.2					R > B	88.2
7	67.6	16.2		8.7	0	7.5					w/in 2%	83.8
8	76.4			12.1		11.5					w/in 2%	76.4
9											-	
10	82.9			6.5		10.9					B > R	82.9
11	72.5	12		7.8	0	7.8					w/in 2%	84.5
12	81.1			8.6		10.3					w/in 2%	81.1
13	80									20	-	80
14	71									29	-	71
15	85.4			7.9		6.7					w/in 2%	85.4
16	78.4									21.6	-	78.4
17	60.4	14.2		8.9	0	16.6					B > R	74.6
18	75.3			3.5		21.2					B > R	75.3
19	85.9									14.1	-	85.9
20	76.4									23.6	-	76.4
21											-	
22	84.2			11		4.8					R > B	84.2
23	81.5			12.1		6.5					R > B	81.5
24	78.2			6.3			6.5	9			B > R	78.2
25	79.5			6			6.7	7.8			B > R	79.5
26	76.6			7.6		15.8					B > R	76.6
27	87			6		7					w/in 2%	87
28											-	
29	83.2									17	-	83.2
30	75.6			6.7		12			5.7		B > R	75.6
31			92.6	7.4							-	
32	80.3			6.6		13.1					B > R	80.3
33	84.4			7.4		8.1					w/in 2%	84.4
M	78.03448	14.78	92.6	8.51875	0	9.802381	6.6	8.4	5.7	20.88333		80.58275862
SD	6.612935			4.432705		4.347254						5.28671306

When the proportions for each lateralization category were compared, we made the following observations:

1) There was consistency in the left-hemisphere lateralization proportions; the mean was 78.0% and the standard deviation was 6.6%. The standard deviation decreased to 5.2% when the proportions for the "incomplete left-hemisphere lateralization" category were added to that of the "left-hemisphere lateralization" category.

2) The means for the proportions of right-hemisphere and bilateral lateralized patients were quite similar: 8.5% and 9.8%, respectively. However, there was much variability in both groups. For example, in Rathore et al. (2009), the right-hemisphere lateralization proportion is almost twice that of the bilateral proportion (i.e., 12.1% and 6.5%). However, in Tracy et al. (2009), the opposite pattern is displayed. The bilateral proportion is almost twice that of the right-hemisphere lateralization proportion (i.e., 15.8% and 7.6%).

The question that arose from this second observation is: Can the variability in the right-hemisphere dominant proportion with respect to the bilateral proportion be explained by the studies' definitions of those categories? To investigate this question, the matrices and corresponding definitions were organized into the following categories: Right greater than bilateral; bilateral greater than right; and right and bilateral within 2.0% (Figure 3A–3C).

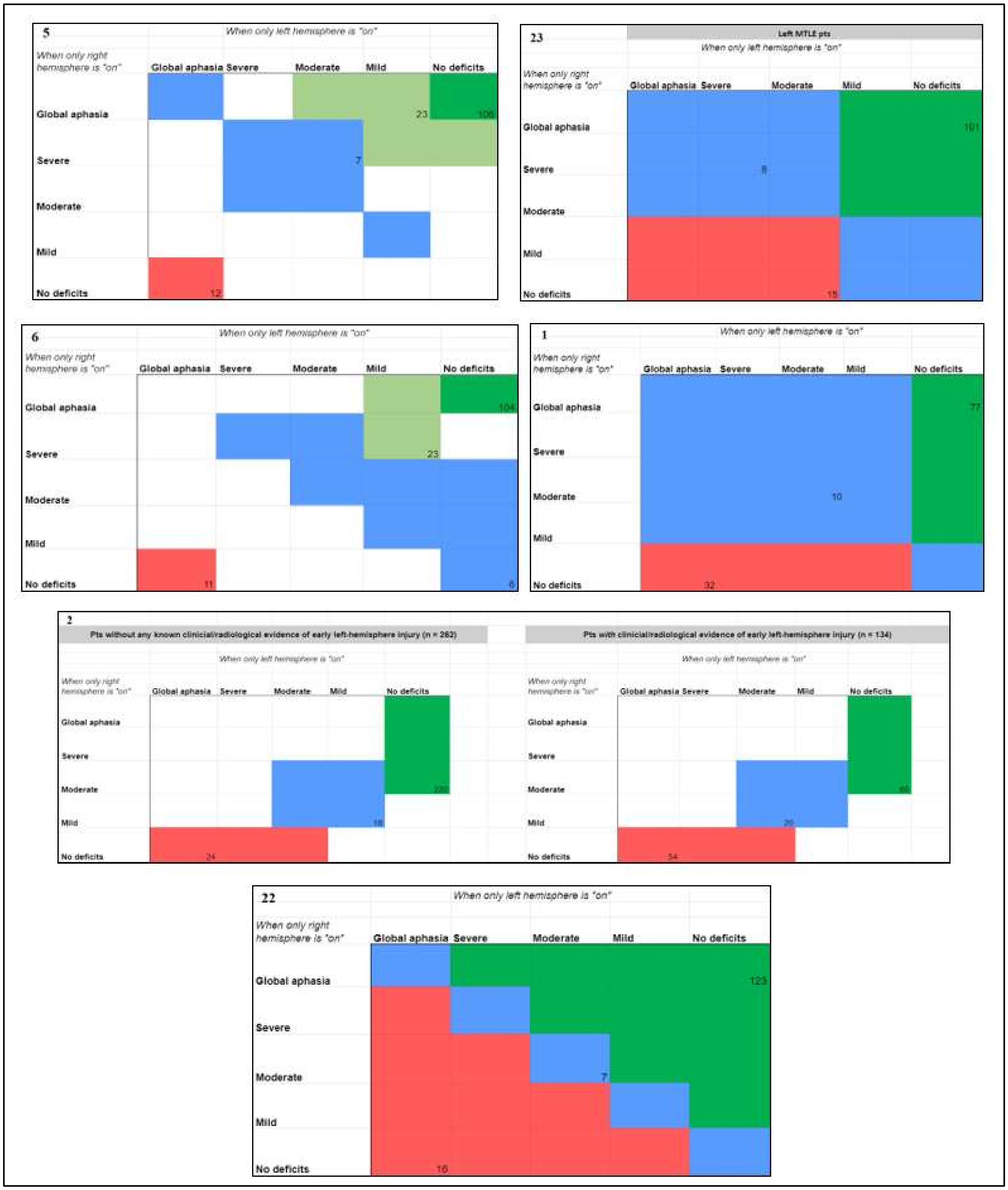


Figure 3A. Proportions of right-hemisphere and bilateral lateralized patients: Right greater than bilateral

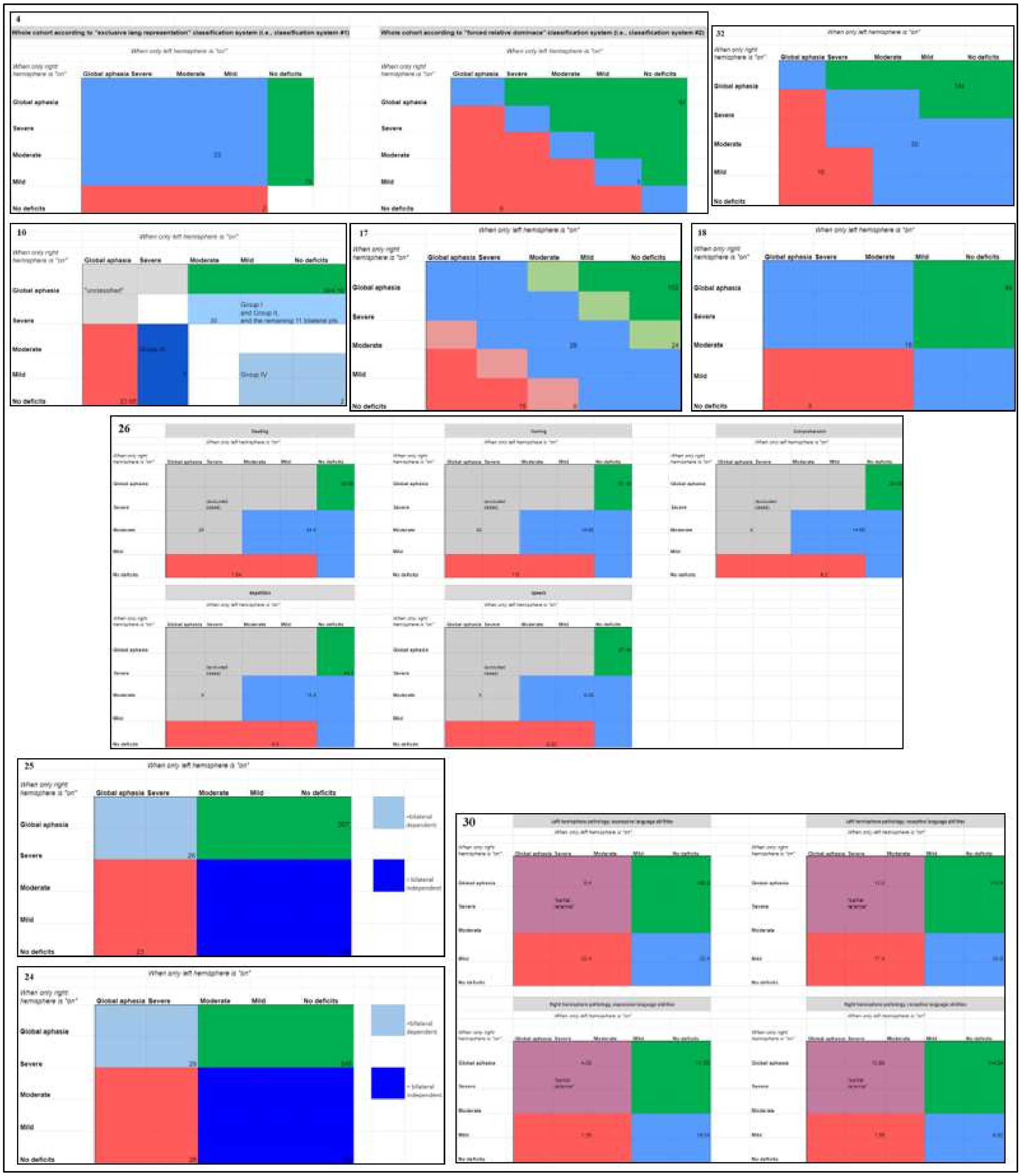


Figure 3B. Proportions of right-hemisphere and bilateral lateralized patients: Bilateral greater than right

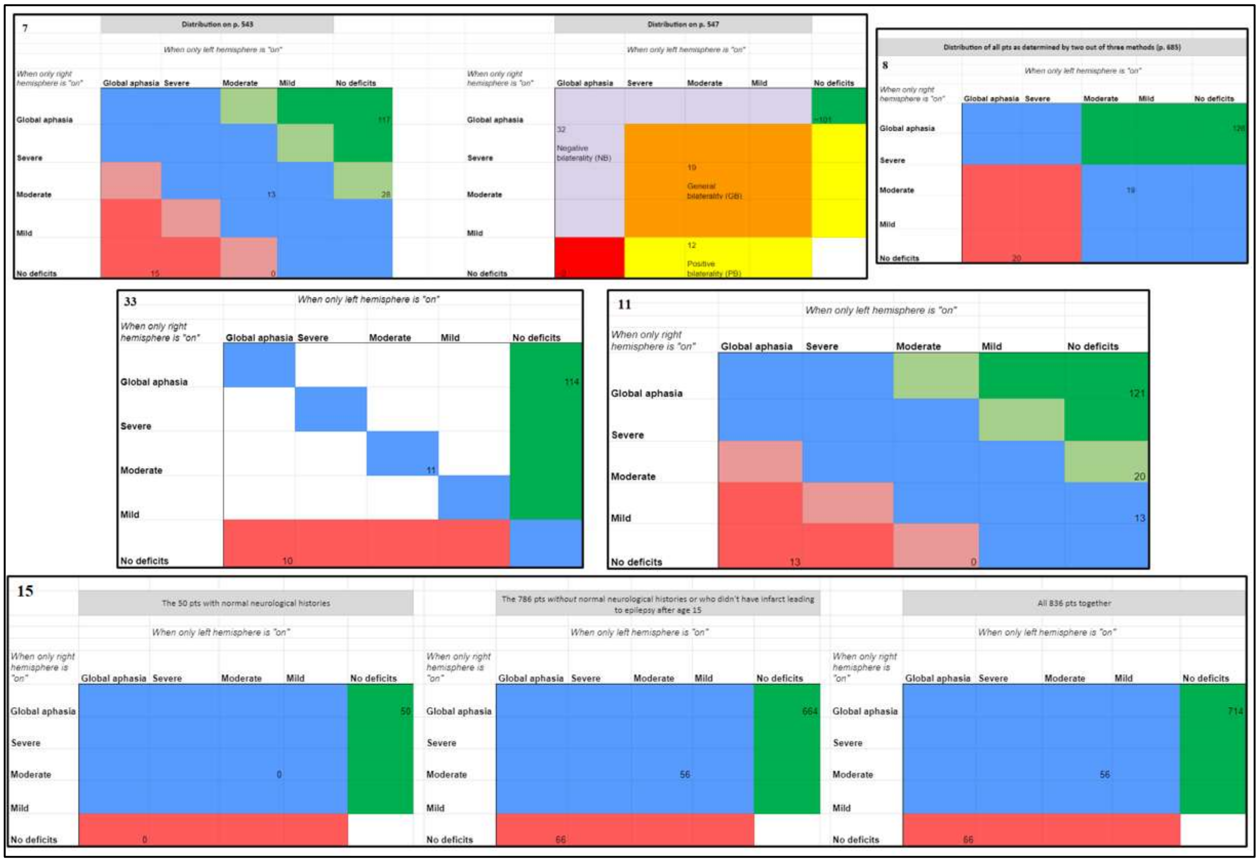


Figure 3C. Proportions of right-hemisphere and bilateral lateralized patients: Right and bilateral within 2.0%

There are some appreciable relationships between the space occupied by different categories on the matrices and the size of the bilateral proportion with respect to the right-hemisphere proportion. For example, in the "bilateral greater than right" group, the bilateral category occupies more cells than the right-hemisphere laterality category in 7.5 out of 9 matrices. The 0.5 represents Loring et al. (1990), in which the proportions of the two distributions were averaged, and the bilateral category occupies more space in one of the matrices and less in the other. The only other matrix that does not conform with this trend is Moser et al. (2011), which includes a unique "partial reliance" category. That "partial reliance" category is defined as "poor performance with each hemisphere," wherein poor performance is defined as performance that is "moderately or severely impaired." This indicates that the patient demonstrated moderately to severely impaired language skills with both injections. Most studies would have considered this behavior to denote a type of bilaterality, in which case it, too, would conform with the trend.

However, in the “right greater than bilateral” group, the right-hemisphere lateralization cells do not occupy more space on the matrix than the bilateral cells, and in the “right and bilateral within 2.0%” group, the right-hemisphere lateralization and bilateral cells do not occupy approximately the same amount of space. Therefore, despite the relationship appreciable in the “bilateral greater than right” group, these three sets of matrices do not explain the way in which the right-hemisphere proportions and bilateral proportions vary.

CHAPTER 4

DISCUSSION

When examining the results of Wada studies, it is critical to remember two matters. Firstly, as the studies mostly involve epilepsy patients, and those patients are not neurotypical, the proportions of patients that fall into the different language lateralization categories may not accurately represent that of the neurotypical population. As Springer et al., 1999 reminds us: “In patients with epilepsy, speech lateralization is more frequently atypical in comparison with healthy people.” The second matter is that there is a great deal of variability across studies with regard to which language tasks are administered, which drugs are used for anesthetization, and how patients are sorted into lateralization categories after language tasks have been administered. Drane et al. (2012) points out that “variability in reported prevalence rates is believed to primarily reflect differences in the implementation of the Wada [procedure] across epilepsy centers, as many institutions have not routinely administered the Wada procedure to all individuals.” Thus, we have reason to believe that the results of these Wada studies may have been different if they had only used neurotypical individuals as participants, but even if they had, the average proportions that emerged from this data may not have been accurate due to low external reliability.

However, taking that into account, we did observe that the standard deviations obtained across the three primary lateralization categories were small: The prevalence of language bilaterality was estimated as 9.8% with an *SD* of 4.3%; the prevalence of left-hemisphere dominance was estimated as 78.0% with an *SD* of 6.6%; and the prevalence of right-hemisphere dominance was estimated as 8.5% with an *SD* of 4.4%. This suggests that there is some consistency across the findings in the 30 articles.

It is also worth noting that among all of the studies, Branch et al. (1964) had the smallest proportion of left-hemisphere dominant patients. They reported it to be 64.7%. When Branch et al. (1964) is removed from the data, and the proportions for the incomplete left-hemisphere lateralization category are added to that of the left-hemisphere lateralization category, the mean proportion of left-hemisphere lateralized patients is 81.1%, and the *SD* is 4.3%. The *SD* is 5.2% when the study is included. Thus, Branch et al.'s findings were markedly disparate from that of the other 29 studies. One variable that could account for this disparateness is the fact that Branch et al. (1964) did not administer the Wada procedure bilaterally in every patient. They periodically categorized a patient as having a certain lateralization after only anesthetizing one hemisphere (i.e., a unilateral Wada administration). This lack of consistent bilateral administration could have caused Branch et al.'s (1964) left-hemisphere dominant proportion to become inflated. The researchers may have anesthetized the patients' left hemispheres, found that language was fully intact with the right hemisphere operating independently, and concluded that those patients had right-hemisphere lateralization. However, it is possible that had the researchers anesthetized the patients' right hemispheres, they would have found that the patients also had some language ability when the left hemisphere was operating independently. Thus, the researchers may have concluded that the patients actually had language bilaterality. Similarly, if Branch et al. (1964) had not required the complete absence of language deficits when the left hemisphere was operating independently to conclude that a patient had left-hemisphere lateralization, some of the patients categorized as having bilaterality would have instead been categorized as having left-hemisphere lateralization.

Regarding the left-hemisphere dominant proportions, we observed that the average proportion—when the incomplete left-hemisphere lateralized category is added in—is highly concordant with the proportion reported in the study with the highest *n*. Loring et al. (1999) had the highest *n*; it was 561. Their left-hemisphere dominant proportion is 81.1%, as compared to the 80.5% mean. Their bilaterality proportion is also similar to the mean: 10.3%, as compared to 9.8%. Thus, again, this study demonstrates surprising consistency given the factors that may compromise the accuracy of Wada studies.

Finally, while no conclusion was drawn about the variation in right-hemisphere lateralization proportions and bilateral proportions from the comparison of matrices, the matrices themselves are wonderfully useful for comparing laterality definitions and gaining an understanding of how definitions may affect distributions. As an example, Loring et al. (1990) provided a distribution for each of their two classification systems and a matrix was generated for each. The first distribution was obtained by way of scores that were assigned during the language tasks. The patients' scores were used to determine whether language impairment was present. Loring et al. (1990) then categorized patients according to the following definitions: left-hemisphere dominance was denoted by language impairment with left hemisphere anesthetization only; right-hemisphere dominance was denoted by language impairment with right hemisphere anesthetization only; and bilateral dominance was denoted by language impairment with both anesthetizations. They were not specific about the degree of impairment that needed to be present in each hemisphere for a patient to be designated as having bilateral dominance, and a patient could be designated as having bilateral dominance regardless of asymmetry of impairment. A patient could show mild deficits when the left hemisphere was acting alone, but then global aphasia when the right was acting alone, and still be considered to have bilateral dominance. This is why the matrix for that Loring et al. classification system has such a large blue, bilateral area (Figure 4; Left).

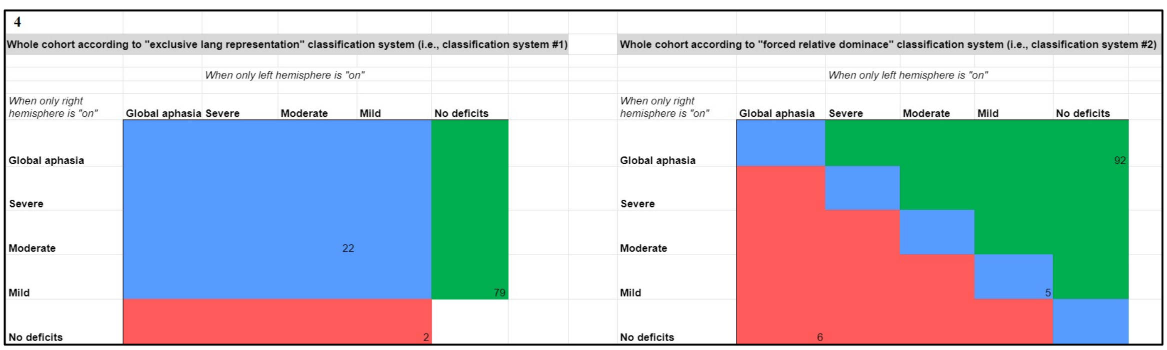


Figure 4. Comparing the Loring et al. (1990) matrices

Loring et al.'s (1990) other classification system used a lateralization index to categorize patients. A lateralization index is an equation into which the scores for the language tasks from each of the two injections is entered. The equation produces a quotient that represents a person's language lateralization on a scale of -1 to 1. In this scale, -1 represents perfect right hemisphere lateralization and 1 represents perfect left hemisphere lateralization. Loring et al. provided ranges for each of their three laterality categories: left-hemisphere dominance is noted by a score ≥ 0.15; right-hemisphere dominance is denoted by a score ≤ -0.15; and bilateral dominance is denoted by a score between -0.15 and 0.15. In the matrix for this classification system (Figure 4; Right), the small bilateral range of -0.15 to 0.15 is reflected visually in the narrow diagonal area that the bilateral category occupies. Loring et al. (1990) actually state that using a lateralization index allows asymmetrical language impairment to assist in classifying a patient as right- or left-hemisphere lateralized. That was lacking in their first classification system, and can be observed in the large swathes of green and red (i.e., left-hemisphere lateralized and right-hemisphere lateralized areas) present in the matrix (Figure 4, Right). In summary, lateralization matrices have the potential to facilitate both analysis and comparison of the systems by which patients are organized into language laterality categories.

CHAPTER 5

CONCLUSION

The 30 Wada studies that were included in our quantitative analysis suggest that the prevalence of language bilaterality is approximately 9.8% in the populations investigated, which were primarily patients with epilepsy. While the analysis of the 26 matrices generated in this study did not yield a clear pattern in matrix configuration and the variance of right-hemisphere lateralization proportions and bilaterality proportions, laterality matrices may still be useful for future research, as they provide a means of graphically comparing disparate definitions of language laterality categories.

REFERENCES

*Study included in review

*Akanuma, N., Alarcón,, G., Lum, F., Kissani, N., Koutroumanidis, M., Adachi, N., Binnie, C. D., Polkey C. E., & Morris, R. G. (2003). Lateralising value of neuropsychological protocols for presurgical assessment of temporal lobe epilepsy. *Epilepsia*, *44*(3), 408–418.

*Benbadis, S. R., Dinner, D. S., Chelune, G. J., Piedmonte, M., & Luders, H. O. (1995). Objective criteria for reporting language dominance by intracarotid amobarbital procedure. *Journal of Clinical and Experimental Neuropsychology*, *17*(5), 682–690.

*Branch C., Milner B., & Rasmussen T. (1964). Intracarotid sodium amytal for the lateralization of cerebral speech dominance; observations in 123 patients. *Journal of Neurosurgery*, *21*(5), 399–405.

*Cunningham, J. M., Morris III, G. L., Drea, L. A., & Kroll, J. L. (2008). Unexpected right hemisphere language representation identified by the intracarotid amobarbital procedure in right-handed epilepsy surgery candidates. *Epilepsy & Behavior: E&B*, *13*(1), 139–143.

*Drane, D. L., Roraback-Carson, J., Hebb, A. O., Hersonskey, T., Lucas, T., Ojemann, G. A., Lettich, E., Silbergeld, D. L., Miller, J. W., & Ojemann, J. G. (2012). Cortical stimulation mapping and Wada results demonstrate a normal variant of right hemisphere language organization. *Epilepsia*, *53*(10), 1790–1798.

Fedio, P., August, A., Patronas, N., Sato, S., & Kufta, C. (1997). Semantic, phonological, and perceptual changes following left and right intracarotid injection (Wada) with a low amytal dosage. *Brain and Cognition*, *33*, 98–117.

*Helmstaedter, C., Brosch, T., Kurthen, M., & Elger, C. E. (2004). The impact of sex and language dominance on material-specific memory before and after left temporal lobe surgery. *Brain: A Journal of Neurology*, *127*(7), 1518–1525.

*Helmstaedter, C., Kurthen, M., Linke, D. B., & Elger, C. E. (1997). Patterns of language dominance in focal left and right hemisphere epilepsies: relation to MRI findings, EEG, sex, and age at onset of epilepsy. *Brain and Cognition*, *33*(2), 135–150.

*Hirata, M., Goto, T., Barnes, G., Umekawa, Y., Yanagisawa, T., Kato, A., Oshino, S., Kishima, H., Hashimoto, N., Saitoh, Y., Tani, N., Yorifuji, S., & Yoshimine, T. (2010). Language dominance and mapping based on neuromagnetic oscillatory changes: comparison with invasive procedures. *Journal of Neurosurgery*, *112*(3), 528–538.

*Isaacs, K. L., Barr, W. B., Nelson, P. K., & Devinsky, O. (2006). Degree of handedness and cerebral dominance. *Neurology*, *66*(12), 1855–1858.

Ishikawa, T., Muragaki, Y., Maruyama, T., Abe, K., & Kawamata, T. (2017). Roles of the Wada test and functional magnetic resonance imaging in identifying the language-dominant hemisphere among patients with gliomas located near speech areas. *Neurologia Medico-Chirurgica*, *57*, 28–34,

*Janecek, J. K., Swanson, S. J., Sabsevitz, D. S., Hammeke, T. A., Raghavan, M., Rozman, M. E., & Binder, J. R. (2013). Language lateralization by fMRI and Wada testing in 229 epilepsy patients: Rates and predictors of discordance. *Epilepsia*, *54*(2), 314–322.

*Janszky, J., Jokeit, H., Heinemann, D., Schulz, R., Woermann, F. G., & Ebner A. (2003). Epileptic activity influences the speech organization in medial temporal lobe epilepsy. *Brain: A Journal of Neurology*, *126*(9), 2043–2051.

*Kamada, K., Sawamura, Y., Takeuchi, F., Kuriki, S., Kawai, K., Morita, A., & Todo, T. (2007). Expressive and receptive language areas determined by a non-invasive reliable method using functional magnetic resonance imaging and magnetoencephalography. *Neurosurgery*, *60*(2), 296–305.

*Keller, S. S., Roberts, N., Baker, G., Sluming, V., Cezayirli, E., Mayes, A., Eldridge, P., Marson, A. G., & Wieshmann, U. C. (2018). A voxel-based asymmetry study of the relationship between hemispheric asymmetry and language dominance in Wada tested patients. *Human Brain Mapping*, *39*(7), 3032–3045.

Knecht, S., Drager, B., Deppe, M., Bobe, L., Lohmann, H., Floel, A., Ringelstein, E., & Henningsen, H. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain*, *123*, 2512–8.

*Kovac, S., Möddel, G., Reinholz, J., Alexopoulos, A. V., Syed, T., Schuele, S. U., Lineweaver, T., & Loddenkemper, T. (2009). Memory performance is related to language dominance as determined by the intracarotid amobarbital procedure. *Epilepsy & Behavior: E&B*, *16*(1), 145–149.

*Kovac, S., Möddel, G., Reinholz, J., Alexopoulos, A. V., Syed, T., Koubeissi, M. Z., Schuele, S. U., Lineweaver, T., Busch, R. M., & Loddenkemper, T. (2010). Visual naming performance after ATL resection: Impact of atypical language dominance. *Neuropsychologia*, *48*(7), 2221–2225.

*Kurthen, M., Helmstaedter, C., Elger, C. E., & Linke, D. B. (1997). Sex differences in cerebral language dominance in complex-partial epilepsy. *Naturwissenschaften*, *84*(3), 131–133.

*Kurthen, M., Helmstaedter, C., Linke, D. B., Hufnagel, A., Elger, C. E., & Schramm, J. (1994). Quantitative and qualitative evaluation of patterns of cerebral language dominance. An amobarbital study. *Brain and Language*, *46*(4), 536–564.

*Kurthen, M., Helmstaedter, C., Linke, D. B., Solymosi, L., Elger, C. E., & Schramm, J. (1992). Interhemispheric dissociation of expressive and receptive language functions in patients with complex-partial seizures: an amobarbital study. *Brain and Language*, *43*(4), 694–712.

Kurthen, M., Linke, D. B., Elger, C. E., & Schramm J. (1992). Linguistic perseveration in dominant-side intracarotid amobarbital tests. *Cortex*, *28*(2), 209–219.

Loring, D. W. & Meador, K. J. (2019). History of the Wada test. The Oxford Handbook of History of Clinical Neuropsychology (W. B. Barr & L. A. Bieliauskas, eds.). DOI: 10.1093/oxfordhb/9780199765683.013.6.

*Loring, D. W., Meador, K. J., Lee, G. P., Murro, A. M., Smith, J. R., Flanigin, H. F., Gallagher, B. B., & King, D. W. (1990). Cerebral language lateralization: evidence from intracarotid amobarbital testing. *Neuropsychologia*, *28*(8), 831–838.

*Loring, D. W., Strauss, E., Hermann, B. P., Perrine, K., Trenerry, M. R., Barr, W. B., Westerveld, M., Chelune, G. J., Lee, G. P., & Meador, K. J. (1999). Effects of anomalous language representation on neuropsychological performance in temporal lobe epilepsy. *Neurology*, *53*(2), 260–264.

Lucke-Wold, B. P., Nguyen, L., Turner, R. C., Logsdon, A. F., Chen, Y. W., Smith, K. E., Huber, J. D., Matsumoto, R., Rosen, C. L., Tucker, E. S., Richter, E. (2015). Traumatic brain injury and epilepsy: Underlying mechanisms leading to seizure. *Seizure*, *33*, 13–23

McElligott, J. (2011). *Wada Test.* Encyclopedia of Clinical Neuropsychology, 2011 edition. https://link.springer.com/referenceworkentry/10.1007%2F978-0-387-79948-3_83.

*Miller, J. W., Dodrill, C. B., Born, D. E., & Ojemann, G. A. (2003). Atypical speech is rare in individuals with normal developmental histories. *Neurology*, *60*(6), 1042–1044.

*Miller, J. W., Jayadev, S., Dodrill, C. B., & Ojemann, G. A. (2005). Gender differences in handedness and speech lateralization related to early neurologic insults. *Neurology*, *65*(12), 1974–1975.

*Möddel, G., Lineweaver, T., Schuele, S. U., Reinholz, J., & Loddenkemper T. (2009). Atypical language lateralization in epilepsy patients. *Epilepsia*, *50*(6), 1505–1516.

*Moser, D. C., Papanicolaou, A. C., Swank, P., & Breier, J. I. (2011). Evidence for the solidarity of the expressive and receptive language systems: A retrospective study. *Journal of the International Neuropsychological Society*, *17*(1), 62–68.

*Papanicolaou, A. C., Simos, P. G., Castillo, E. M., Breier, J. I., Sarkari, S., Pataraia, E., Billingsley, R. L., Buchanan, S., Wheless, J., Maggio, V., & Maggio, W. W. (2004). Magnetocephalography: a noninvasive alternative to the Wada procedure. *Journal of Neurosurgery*, *105*(5), 867–876.

Passarelli, V., Pinto, L. F., Jorge, C. L., Puglia, P., Adda, C. C., Wen, H., & Castro, L. H. (2014). The intracarotid etomidate Wada test: A 54-patient series. *Epilepsy & Behavior*, *39*, 73–77.

*Rasmussen, T. & Milner, B. (1977). The role of early left-brain injury in determining lateralization of cerebral speech functions. *Annals of the New York Academy of Sciences*, *299*(1), 355–369.

*Rathore, C., George, A., Kesavadas, C., Sarma, P. S., & Radhakrishnan, K. (2009). Extent of initial injury determines language lateralization in mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS). *Epilepsia*, *50*(10), 2249–2255.

*Risse, G. L., Gates, J. R., & Fangman, M. C. (1997). A reconsideration of bilateral language representation based on the intracarotid amobarbital procedure. *Brain and Cognition*, *33*(1), 118–132.

Springer, J. A., Binder, J. R., Hammeke, T. A., Swanson, S. J., Frost, J. A., Bellgowan, P. S., Brewer, C. C., Perry, H. M., Morris, G. L., Mueller, W. M. (1999). Language dominance in neurologically normal and epilepsy patients. *Brain*, *122*, 2033–2046.

*Tracy, J. I., Waldron, B., Glosser, D., Sharan, A., Mintzer, S., Zangaladze, A., Skidmore, C., Siddiqui, I., Caris, E., & Sperling, M. R. (2009). Hemispheric lateralization and language skill coherence in temporal lobe epilepsy. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *45*(10), 1178–1189.

*Uijl, S. G., Leijten, F. S. S., Arends, J. B. A. M., Parra, J., van Huffelen, A. C., van Rijen, P. C., & Moons, K. G. M. (2009). The intracarotid amobarbital or Wada test: unilateral or bilateral? *Acta Neurologica Scandinavica*, *119*(3), 199–206.

University of British Columbia. (2019*). Congratulations to Dr. Juhn Wada, Professor Emeritus in the Department of Psychiatry and Neurosciences on his induction into the Hall of Honor at Vancouver General Hospital*. Faculty of Medicine, Department of Psychiatry. https://psychiatry.ubc.ca/2019/02/07/32469/.

Wada, J. (1949). A new method for the determination of the side of cerebral speech dominance. A preliminary report of the intra-carotid injection of sodium amytal in man (Vol. 14, pp. 221–222). Tokyo: Igaku to Seibutsugaki.

Wegrzyn, M., Mertens, M., Bien, C. G., Woermann, F. G., & Labudda, K. (2019). Quantifying the confidence in fMRI-based language lateralisation through laterality index deconstruction. *Frontiers in Neurology*, *10*(655), 1–15.

*Woermann, F. G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., Okujava, M., Wolf, P., Tuxhorn, I., & Ebner, A. (2003). Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology*, *61*(5), 699–701.

*Woods, R. P., Dodrill, C. B., & Ojemann, G. A. (1988). Brain injury, handedness, and speech lateralization in a series of amobarbital studies. *Annals of Neurology*, *23*(5), 510–518.

APPENDIX

1. **Article**: Intracarotid sodium amytal for the lateralization of cerebral speech dominance; observations in 123 patients

   Authors: Branch C, Milner B, & Rasmussen T.

   Handedness:

   Left-handed: 51

   Right-handed: 48

   Ambidextrous: 20

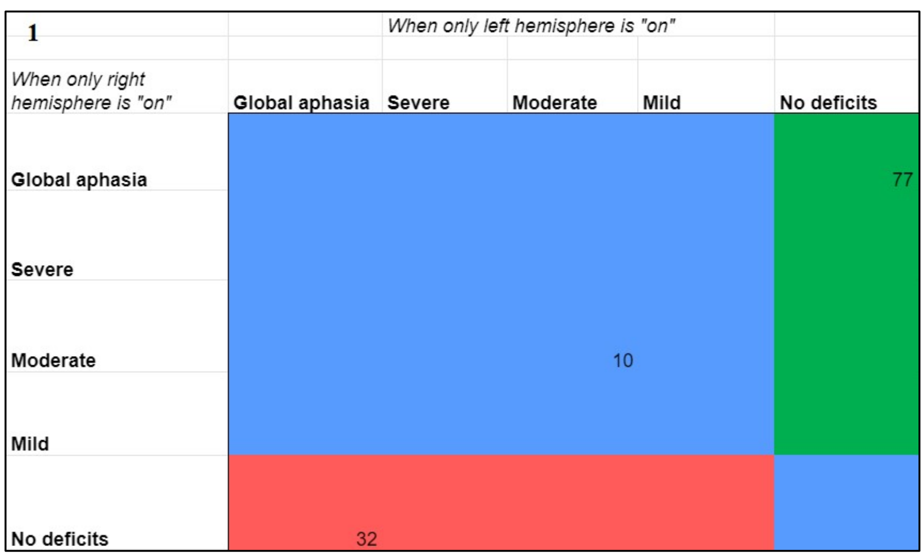
   Qualifying condition: All participants but one had focal cerebral seizures. In 102 of the participants the seizures were secondary to cerebral cicatrix; in 12, the seizures were secondary to neoplasms (10 with glioma and two with meningioma); in seven, the seizures were secondary to arteriovenous malformations; and in one, the seizures were associated with a subdural cyst within the middle fossa. The participant without seizures had a thalamic tumor in their left hemisphere. All participants were either left-handed, ambidextrous, or right-handed and presenting with "some clinical clue" that "cast doubt" on the lateralization.

   Radiological evidence of brain lesion: p. 402, third paragraph on the right side of the page, and Table 8 on p. 403. The researchers only report on evidence of early brain damage for the left-handed and ambidextrous patients. In that group of 71 patients, 27 had clinical evidence of early left brain damage (dating from birth or the first five years of life) and 44 had no evidence of early left brain damage.

   Lateralization categories source: pp. 401–402. Regarding left-hemisphere and right-hemisphere dominance, this is all that is said: "In cases of carotid injection into the nondominant hemisphere, contralateral hemiparesis and hemianopsia are produced without interference with speech" (p. 401). Regarding bilateral dominance, the paper only gives case examples to explain why some patients were designated as bilateral. For example, a patient had "postoperative dysphasia following the removal of Broca's area in what was thought to be the nondominant hemisphere." The same patient had "marked dysphagia with injection of Amytal into the contralateral hemisphere preoperatively." That's why they designate the patient as bilateral.

Distribution source: p. 402, Table 6. The quantities in the columns for "Left, "Bilateral," and "Right" were added.

Matrix composition rationale: The phrase “without interference with speech” was mapped as “no deficits” on the matrix, so right-hemisphere dominant would consist of “no deficits” when the left hemisphere is anesthetized and vice versa for right-hemisphere dominance. As the article does not discuss the abilities of the non-dominant hemisphere, we assumed that they should range from “mild deficits” to “global aphasia.” If they ranged all the way to “no deficits,” that hemisphere would instead be considered the dominant hemisphere, according the definition of ‘dominant hemisphere’ the authors presented. Finally, as the article does not define bilaterality, every remaining cell was considered a potential bilateral criterion.



2. **Article:** The role of early left-brain injury in determining lateralization of cerebral speech functions

Authors: Rasmussen, T. & Milner, B.

Handedness:

<u>For the 262 patients without any known clinical/radiological evidence of early left-hemisphere injury</u>*:*

Left-handed or ambidextrous: 122

Right-handed: 140

Found on p. 358, in Table 1.

<u>For the 134 patients that had definite evidence of early left hemisphere damage</u>:

Left-handed or ambidextrous: 92

Right-handed: 42

Found on p. 359, in Table 2.

Qualifying condition: All patients had medically intractable focal epilepsy. They were either left-handed or ambidextrous, or right-handed and demonstrated "some hint" that speech may not be represented in the left hemisphere.

Radiological evidence of brain lesion: The 262 patients do not have "any known clinical or radiologic evidence of an early left-hemisphere injury" (p. 357, in the "Patient Sample" section). The 134 patients had "epileptogenic lesions " that were "all incurred before the age of 6 and in most instances dated from the perinatal period." (p. 357, in the "Patient Sample" section).

Lateralization categories source:

<u>For the 262 patients without any known clinical/radiological evidence of early left-hemisphere injury</u>*:*

pp. 357–358. Regarding right-hemisphere dominance and left-hemisphere dominance, the article states the following: "If the injected hemisphere is non-dominant for speech the patient continues to count and to carry out the verbal tasks while the temporary flaccid hemiparesis is present. Some patients stop counting temporarily for a period of up to 20–30 seconds, but resume normal speech with urging. [...] When the injected hemisphere is dominant for speech, the patient

typically stops talking near the end of the injection and remains completely aphasic, or markedly dysphasic, until the recovery of the hemiparesis is well along, usually 4–10 minutes." (p. 357) Regarding bilateral dominance, the article states the following: "the speech deficits were mild, from both the right- and left-sided injections, although the mean duration of contralateral hemiparesis was the same as for the cases classed as unilateral. In a half of these patients, speech was not arrested by either the right or left injection, but clear dysphasic responses were obtained with each. In the other half, in whom speech was temporarily arrested by the injection, the duration of the arrest was significantly shorter than the speech arrest from injection of the language-dominant hemisphere of patients with unilateral speech representation." (p. 358)

For the 134 patients that had definite evidence of early left hemisphere damage:

The description for right-hemisphere and left-hemisphere dominance are the same here, but the researchers offer further description for the bilateral category, so we are including it here. They state that "speech was disturbed in both injections" for bilateral patients. (p. 359)

Distribution source:

For the 262 patients without any known clinical/radiological evidence of early left-hemisphere injury: p. 358, Table 1.

For the 134 patients that had definite evidence of early left hemisphere damage: p. 359, Table 2.

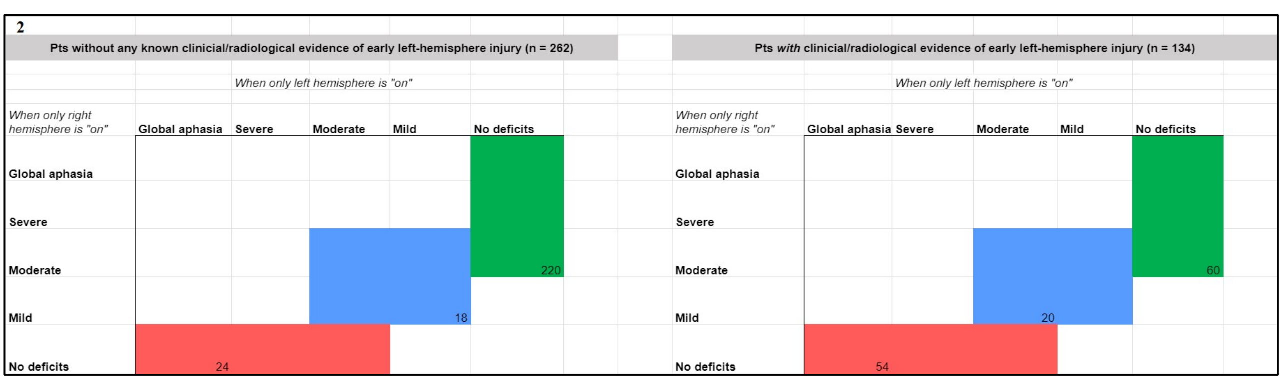
Matrix composition rationale:

For the 262 patients without any known clinical/radiological evidence of early left-hemisphere injury:

For the left-and right-hemisphere dominant categories, we are not considering the 20–30 second discontinuation of counting that sometimes occurs when the non-dominant hemisphere is injected as evidence that the active hemisphere has mild impairment; we are simply considering that to be a temporary effect of the body adjusting to the recently-injected anesthetic. So, we did not include the "mild deficits" category in the area for the dominant hemisphere (i.e., did not include "mild deficits" in the left-hemisphere dominant area on the horizontal axis). Regarding the non-dominant hemisphere, we decided that the description of "stops talking near the end of the injection and remains completely aphasic, or markedly dysphasic" maps onto the matrix categories of "moderate deficits" to "global aphasia." We did not include the "mild deficits" cells in those areas because we do not believe that this definition describes mild deficits. Finally, regarding the bilateral cells, the description "the speech deficits were mild, from both the right- and left-sided injections" maps onto the "mild deficits" for both right and left hemisphere cell. We decided that the bilateral description "speech was not arrested by either the right or left injection, but clear dysphasic responses were obtained with each" maps onto that same cell (i.e., mild for both hemispheres), and the bilateral description "the duration of the arrest was significantly shorter than the speech arrest from injection of the language-dominant hemisphere of patients with unilateral speech representation" maps onto "moderate deficits," as the fact that a person was not able to speak at all (beyond the 20–30 second speech arrest that was present even when the dominant hemisphere was active) constitutes a moderate deficit. Thus, the bilateral area includes both the "mild deficits" and "moderate deficits" categories for both hemispheres.

<u>For the 134 patients that had definite evidence of early left hemisphere damage</u>:

Our rationale here is identical to that of the first matrix, as the bilateral description "speech was disturbed in both injections" is compatible with the previous bilateral descriptions. We decided that there was no reason to alter the bilateral area, as this description does not augment or conflict with the previous ones.



3. **Article**: Brain injury, handedness, and speech lateralization in a series of amobarbital studies

   Authors: Woods, R. P., Dodrill, C. B., & Ojemann, G. A.

   Handedness:

   Left-handed: 36

   Right-handed: 162

   Note: Those numbers add to 198. A possible explanation for that number not being 208 or 197 is that the authors state, "Handedness of patients who did not undergo neuropsychological testing was classified as unknown."

   Qualifying condition:

   - 197 patients (of the 208 patients that underwent Wada) were preparing for a resection of epileptic foci.
   - Of the 208 patients that underwent Wada, 10 had history of right hemiparesis, six had history of left hemiparesis, and 192 had no history of hemiparesis. (While not an inclusion criterion, history of hemiparesis was a factor the authors took special note of).
   - Of the original 237 patients, 15 patients were excluded because they'd undergone cortical resection and three patients were excluded because they had history of aphasia or CVA as adults without associated hemiparesis.

   Radiological evidence of brain lesion: "Radiological studies reviewed included pneumoencephalograms, computed tomographic scans of the head, metrizamide-enhanced computed tomographic scans, and magnetic resonance imaging scans of the head. Studies were classified as abnormal if they showed any abnormality outside the temporal lobe. Lesions confined to the temporal lobe were fairly common, since many of these patients suffer from temporal lobe epilepsy, and radiological studies other than angiograms showing such abnormalities were classified as normal. Radiological studies were classified as unknown if no radiological reports were available." (p. 511, in "Methods and Patients"). The lesion numbers can likely be calculated from Table 1 on p. 512 by adding the numbers in the "Lesion Side" section. However, note that while 208 patients underwent Wada, those numbers only add to 201. No explanation for this could be found.

Lateralization categories source: p. 511, last sentence of the top paragraph on the right, and second to last sentence of the last paragraph on the left. The researchers never explain how they determine which patients are placed in which lateralization categories. These two sentences are the only ones that address their lateralization decisions: "language was tested by asking the patient to name objects and to read sentences aloud" and "studies in which both carotids were not injected were considered incomplete for the purposes of this study."

Distribution source: p. 512, by adding the "Atypical" and "Left" columns under the "Speech" setting in Table 1.

Matrix composition rationale: No matrix could be built.

Note: No matrix could be built for this article, but its distribution information was included in the quantitative analysis.

4. **Article**: Cerebral language lateralization: evidence from intracarotid amobarbital testing

   Authors: Loring, D. W., Meador, K. J., Lee, G. P., Murro, A. M., Smith, J. R., Flanigin, H. F., Gallagher, B. B., & King, D. W.

   Handedness:

   Left or "mixed" handed: 12

   Right-handed: 91

   Qualifying condition: All patients undergoing epilepsy surgery. Patients could not have radiological lesions in any area but the temporal lobe.

   Radiological evidence of brain lesion: See above. There were 103 patients in total (n = 103), and of those patients, 86 patients did not have evidence of early brain injury prior to 2 years of age, and 69 patients did not have evidence of early brain injury prior to 6 years of age.

Lateralization categories source: P. 833, the last two paragraphs in the "Language Rating" section. The first classification system defines the categories as follows: "Language impairment following both injections was classified as bilateral language representation regardless of relative asymmetry of language impairment. Language deficits following a single injection only were classified as unilateral cerebral dominance (i.e., exclusive language representation)." The second classification system defines the categories as follows: "...language dominance was based upon relative language impairment. A patient who displayed bilateral language impairment, but with a greater deficit following a single injection, was classified as language dominance for the hemisphere with greater linguistic failure. Patients were classified as having bilateral language only when a side of greater representation could not be established. To determine language asymmetry, the sum of language ratings was calculated for each side, and laterality ratios were computed (i.e., L - R, L + R). For example, patients with errors following left hemisphere injection only received scores of +1.0, and patients with errors only following right hemisphere injection scores of -1.0. Subjects with laterality ratios greater than 0.15 or less tha -0.15 were classified as having either left or right language dominance, whereas patients with laterality scores between 0.15 and -0.15 were classified as bilateral language with no asymmetry."

Note: Language impairment is defined in p. 833 in the second paragraph in the "Language Rating" section: "...one of two error configurations had to be detected. In the first, impairments (scores > 0) had to be present in at least two categories, with one of the scores greater than 1. In the second pattern, language representation was inferred if at least 3/4 language categories were only mildly impaired (e.g., scores of 1).

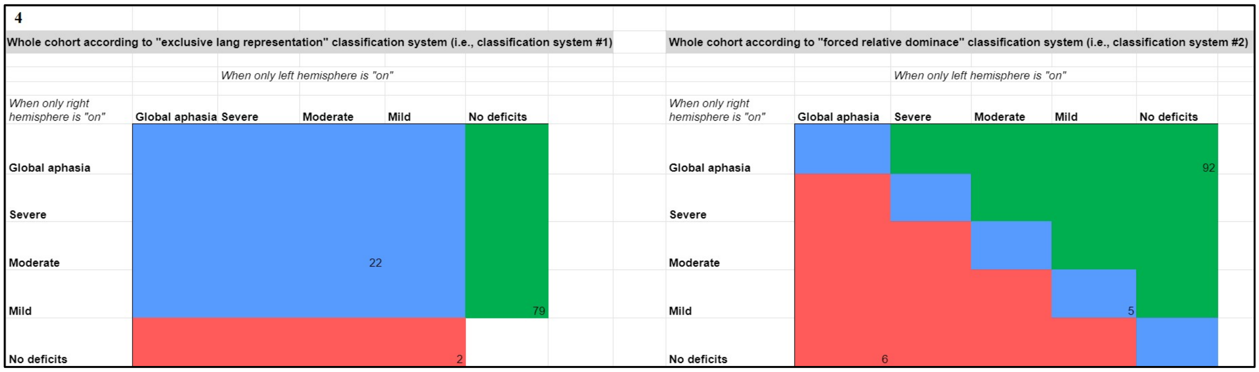
Distribution source: P. 835, in the "Exclusive language representation" and "Forced relative dominance" rows in Table 1. The former is classification system #1; the latter is classification system #2.

Matrix composition rationale:

<u>Classification System #1</u>: Unilateral dominance was defined as the patient demonstrating

language deficits with only one injection, and the nature of those deficits are not specified, so we're assuming that they could range from mild to global aphasia. Thus, right hemisphere dominance is represented by the patient demonstrating mild deficits to global aphasia when only the left hemisphere is active, and then no deficits when only the right hemisphere is active. Left hemisphere dominance is represented by the reverse. Bilateral dominance is represented by deficits following both injections, regardless of the severity of the deficits or the asymmetry of the deficits. Thus, every remaining cell in the matrix, save the cell on which the "No deficits" cell and row converge, is designated as bilateral.

Classification System #2: For a patient to be designated as having right hemisphere dominance, their deficits when the right hemisphere was anesthetized had to be greater than their deficits when the left hemisphere was anesthetized. Since the amount of this required difference was quite small (i.e., the patient needed to have less than -0.15 on the ratio [L - R / L + R], calculated with their language scores on each injection), we interpreted it as a one-unit difference on the matrix. In other words, if a patient had mild deficits when the left hemisphere was acting alone and no deficits when the right hemisphere was acting alone, they would be designated as having right hemisphere dominance. Likewise, if they had global aphasia when the left hemisphere was acting alone and severe deficits when the right hemisphere was acting alone, they would be designated as having right hemisphere dominance. For a patient to be designated as having bilateral dominance, they would have to have complete symmetry of deficits with each injection. This is why the bilateral cells run across the matrix in a one-cell, diagonal line.



5. **Article**: Linguistic perseveration in dominant-side intracarotid amobarbital studies

   Authors: Kurthen, M., Linke, D. B., Elger, C. E., & Schramm, J.

   Handedness:

   Right-handed: 121

   Left-handed: 23

   Ambidextrous: 4

   Qualifying condition: All patients had long-standing, medically intractable complex-partial seizures.

   Radiological evidence of brain lesion: Researchers only describe lesions (as identified through MRI and CCT) in a subset of 21 patients. Within that subset, three patients had right temporal lesions, four had left temporal lesions, and three had right frontal lesions. (p. 212, Table 1)

   Lateralization categories source: p. 211, second paragraph from the top. The researchers provide the following definitions: "**(a)** and **(b)**: Complete left-(right) hemisphere dominance (CLD/CRD) as indicated by a complete failure in tasks (1) to (5) in the initial period of left (right) IAT and a dysphasic period afterwards; absence of language deficits in right (left) IAT. **(c)**: Incomplete left-hemisphere dominance (ILD) was diagnosed with occurrence of one of the following patterns of performance: **(1)** complete loss of speech functions in left IAT and incomplete loss of speech functions—as indicated by an impaired performance in at most three tasks—in right IAT. **(2)** Severe, but incomplete loss—as indicated by a lack of adequate responses in three or four tasks—in left IAT and absence of language disturbances in right IAT. **(3)** Severe, incomplete loss of speech functions in left IAT and minor language disturbances—as indicated by an impaired performance in one or two tasks—in right IAT. **(d)**: Genuinely bilateral language representation (BR). To be classified as "BR," a patient had to perform in either of two ways: **(1)** complete or predominant loss of expressive language functions in one IAT and loss of receptive functions in the other; **(2)** symmetrical disturbance of expressive and receptive functions in both IAT's." This was rephrased as follows to facilitate matrix building:

Left hemisphere lateralization: Complete failure in all five language tasks in the initial period of Wada procedure (when left hemisphere anesthetized) and a dysphasic period afterwards. Also, an absence of language deficits when the right hemisphere is anesthetized.

Right hemisphere lateralization: Complete failure in all five language tasks in the initial period of Wada procedure (when right hemisphere anesthetized) and a dysphasic period afterwards. Also, an absence of language deficits when the left hemisphere is anesthetized.

"Incomplete" left hemisphere lateralization: One of the following patterns: (1) Complete failure in all five language tasks when left hemisphere anesthetized; impaired performance in at most three language tasks when right hemisphere anesthetized. (2) Failure of three or four tasks when left hemisphere anesthetized; no language disturbance when right hemisphere anesthetized. (3) Failure of three or four tasks when left hemisphere anesthetized; impaired performance in one or two tasks when right hemisphere anesthetized.

Bilateral lateralization: One of the following patterns: (1) "Complete or predominant loss of expressive language functions in one IAT and loss of receptive functions in the other" (2) "Symmetrical disturbance of expressive and receptive functions in both IATs."

Distribution source: p. 211, first paragraph under the "Results" section. Complete left-hemisphere dominance: 106; complete right-hemisphere dominance: 12; incomplete left-hemisphere dominance: 23; genuinely bilateral language representation: 7.

Matrix composition rationale: Right hemisphere dominance is denoted by "No Deficits" when only the right hemisphere is active and "Global Aphasia" (i.e., complete failure in tasks 1–5 with a dysphasic period afterwards) when only the left hemisphere was active. Left hemisphere dominance is denoted by the reverse of this. Incomplete hemisphere dominance encompassed a variety of patient presentations. The first presentation the researchers describe (i.e., #1 in the "c" section) is denoted by complete loss of speech functions when only the right hemisphere is active, which we denoted as "Global Aphasia" on the matrix, along with impaired performance in 1 to 3 of the 5 tasks, which we denoted as "Mild Deficits" and "Moderate Deficits" on the matrix. The second presentation the researchers describe (i.e., #2 in the "c" section) is denoted by severe deficits when only the right hemisphere is active (indicated by "inadequate performance" in 3 to 4 of the 5 tasks), which we represented as "Severe" on the matrix, paired with no deficits when the left hemisphere is active. The third presentation the researchers describe (i.e., #3 in the "c" section) is also denoted by severe deficits when only the right hemisphere is active, which we represented as "Severe" on the matrix, paired with impaired performance on one to two tasks of the five when the left hemisphere is active, which we represented as "Mild Deficits" on the matrix. Finally, the researchers describe bilateral language dominance as being one of two patient presentations. In the first presentation they describe (i.e., #1 in the "d" section), the patient has complete or "predominant" loss of expressive abilities when one hemisphere is anesthetized and loss of receptive abilities when the other is anesthetized. We decided that this should be represented by "Moderate Deficits" when the right hemisphere is active with "Severe Deficits" when the left hemisphere is active, as well as the reverse. (Note: There is no way to clearly represent the loss of expressive abilities versus receptive abilities on the matrix. We chose to designate these cells this way because we felt it was preferable to not representing this presentation on the matrix at all). In the second presentation the researchers describe (i.e., #2 in the "d" section), they patient has symmetrical impairment of receptive and expressive language abilities for both anesthetizations. This is represented by symmetrical deficits when each hemisphere is anesthetized. The cell in which the "No Deficits" row and column converge is left blank, as the researchers specify that bilaterality necessitates deficits for each hemisphere. Note: The matrix on the right incorporates the researcher's descriptions of the various presentations. The matrix on the left condenses the presentations into their overall groups.

5	*When only left hemisphere is "on"*				
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia				23	106
Severe			7		
Moderate					
Mild					
No deficits	12				

6. **Article**: Interhemispheric dissociation of expressive and receptive language functions in patients with complex-partial seizures: an amobarbital study

   Authors: Kurthen, M., Helmstaedter, C., Linke, D. B., Solymosi, L., Elger, C. E., & Schramm, J.

   Handedness:

   Right-handed: 119

   Left-handed: 21

   Ambidextrous: 4

   Qualifying condition: Long-standing, medically intractable complex-partial seizures. All were submitted to IAP as part of a presurgical evaluation.

   Radiological evidence of brain lesion: Researchers do not state how many, if any, of their patients had brain lesions. However, it's implied that some patients may have: "In four (2.8%) of these patients—all right-handers with early onset of epilepsy and/or evidence of early brain damage—there was strong evidence of an interhemispheric dissociation of expressive and receptive language functions." (p. 694)

Lateralization categories source: p. 698–699, in the first paragraph of the "Results" section. The researchers define unilateral dominance as the anesthetization leading to "a complete loss of language functions in the initial period of maximal amobarbital action, while IAP on the nondominant side revealed no definite language deficits." They define incomplete left hemisphere dominance as "complete or at least severe loss of speech functions in left IAP and minor language disturbances in right IAP. That is, some language subfunctions appeared to be doubly represented in the left and right hemisphere, but there was no major interhemispheric dissociation of functions." Finally, the researchers define "genuine" bilateral dominance as there being "major contributions of both hemispheres to linguistic performance." This could be manifested as a patient having receptive functions intact for both anesthetizations but expressive functions more intact for right hemisphere anesthetizations, and or an interhemispheric dissociation between expressive and receptive functions.

This was rephrased to facilitate matrix building: <u>Left-hemisphere dominance</u>: Anesthetization of left hemisphere led to "a complete loss of language function in the initial period of maximal amobarbital action," while anesthetization of the right hemisphere "revealed no definite language deficits." <u>Right-hemisphere dominance</u>: Anesthetization of right hemisphere led to "a complete loss of language function in the initial period of maximal amobarbital action," while anesthetization of the left hemisphere "revealed no definite language deficits." <u>Bilateral dominance</u>: There were "major contributions of both hemispheres to linguistic performance." (They called these patients "genuinely bilateral").

<u>Case Studies</u>:

#1: Right hemisphere had expressive abilities; left hemisphere had receptive abilities. Left IAP: Counting intact, repetition intact, and patient pressed investigator's hand on command, but naming, reading, and pointing to objects not intact. Paraphasia in reading task. No typical dysphasic period as drug faded. Right IAP: Naming, reading, and repetition not intact, but pointing to objects intact. Typical dysphasic period as drug faded. (p. 700)

#2: Right hemisphere had receptive abilities; left hemisphere only had spontaneous speech (i.e., irrelevant comments). Left IAP: Counting, naming, "spontaneous speech" and repeating not intact, but pointing to objects and raising arm on command intact. Typical dysphasic period as drug fades. Right IAP: Counting, pointing, naming, raising arm on command, and repetition not intact. The patient did speak spontaneously some (e.g., "I have to go to the lavatory"). No typical dysphasic period as drug faded. (p. 703)

#3: "The complementary performance in tasks (1) and (2) indicates a left-hemispheric representation of expressive and a right-hemispheric representation of receptive language functions." Left IAP: Counting, reading, and repetition not intact; pointing to objects, raising arm on command, naming, and some spontaneous speech intact. Typical dysphasic period as drug faded. Right IAP: Counting (for a little while) was intact; the patient could not be directed to any other tasks. No typical dysphasic period as drug faded. (p. 704)

#4: "Left-hemispheric dominance for receptive language functions (as again indicated by complementary performance in tasks (1) and (2)...evidence of right-hemispheric dominance for expressive functions." Left IAP: Counting intact ("could not be stopped"), and reading and naming were "testable" (authors not clear on whether they were intact). Receptive abilities not intact. No typical dysphasic period as drug faded. Right IAP: Counting and expressive language abilities not intact ("except for two successful trials in naming"), and reading and repetition "couldn't be performed," but pointing to objects was intact. Typical dysphasic period as drug faded. (p. 706) Incomplete left-hemisphere dominant: [A subset of the bilateral category] Patients "showed complete or at least severe loss of speech functions" when left hemisphere was anesthetized and "minor language disturbances" when right hemisphere was anesthetized.

Distribution source: p. 698, in the first paragraph of the "Results" section. Left-hemisphere dominance: 104; right hemisphere dominance: 11; incomplete left hemisphere dominance: 23; "genuine" bilateral dominance: six (with two having receptive functions intact for both anesthetizations but expressive functions more intact for right hemisphere anesthetizations, and 4 having interhemispheric dissociation between expressive and receptive functions).

Matrix composition rationale: The researchers definition of unilateral dominance as "a complete loss of language functions in the initial period of maximal amobarbital action, while IAP on the nondominant side revealed no definite language deficits" corresponds with the matrices' "No Deficits" category for the hemisphere of dominance and "Global Aphasia" category for the non-dominant hemisphere. This is why the right hemisphere dominance and left hemisphere dominance sections each constitute only one cell. As the researchers define incomplete left hemisphere dominance as "complete or at least severe loss of speech functions in left IAP and minor language disturbances in right IAP," this section is represented by "Mild Deficits" when the left hemisphere is active and "Severe Deficits" and "Global Aphasia" when the right hemisphere is active. Lastly, as the researchers define bilateral dominance as there being "major contributions of both hemispheres to linguistic performance," we decided that the bilateral dominance section could not include the "Global Aphasia" column or row. Each hemisphere had to have some language ability independently. Further, we translated the scenario in which a patient had receptive functions intact for both anesthetizations but expressive functions more intact for right hemisphere anesthetizations as the cells for which the left hemisphere demonstrated less deficits than the right hemisphere (leaving out all "Global Aphasia" cells). For example, this would include the cell in which the left hemisphere had "Mild Deficits" but the right hemisphere had "Moderate Deficits." Then we translated the scenario in which a patient demonstrated interhemispheric dissociation between expressive and receptive functions as the cells in which the left hemisphere and right hemisphere displayed the same degree of deficits (e.g., the cell in which the "Mild Deficits" row and column converge). Thus, the bilateral dominance section consists of all the cells for which the left hemisphere demonstrated less deficits than the right (leaving out any cells that have a "Global Aphasia" row or column) and all the cells in which the left and right hemisphere displayed the same degree of deficits. (Note: The cell in which the "No Deficits" row and column converges is included in the bilateral section because the researchers did not specify that impairment needed to be present for this categorization).

6	*When only left hemisphere is "on"*				
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					104
Severe				23	
Moderate					
Mild					
No deficits	11				6

7. **Article**: Quantitative and qualitative evaluation of patterns of cerebral language dominance

   Authors: Kurthen, M., Helmstaedter, C., Linke, D. B., Hufnagel, A., Elger, C. E., & Schramm, J.

   Handedness:

   Right-handed: 142

   Left-handed: 25

   Ambidextrous: 6

   Qualifying condition: 170 of the 173 patients had long-standing, medically intractable complex-partial seizures. The remaining three were undergoing tumor resection.

Radiological evidence of brain lesion: p. 538, in "Patients and Clinical Assessment" section. Morphological lesions were detected in 112 (65%) patients by MRI or CCT (50 right, 51 left, 11 bilateral, subcortical, or generalized).

Lateralization categories source: pp. 539-540. The researchers use an LI equation to sort patients into laterality categories. The equations is L = [(ScoreIAPRight - Score IAPLeft) / (ScoreIAPRight + ScoreIAPLeft)] x (n/m). The researchers' LI ranges are: 0.85 to 0.5 for incomplete left-hemisphere dominance; 0.5 to -0.5 for strong bilaterality; -0.5 to -0.85 for incomplete right-hemisphere dominance; 0.85 to 1 for left-hemisphere dominance; and -0.85 to -1 for right-hemisphere dominance. These are the five dominance subpatterns, further described:

<u>Complete left-hemisphere dominance (CLD)</u>: Complete failure in all language tasks during the initial period of left hemisphere anesthetization and a dysphasic period afterward; in right hemisphere anesthetization there should be no language deficits. When taking their lateralization index quotients into account, they said that a quotient of 0.85 to 1 is left-dominant (LD).

<u>Complete right-hemisphere dominance (CRD)</u>: Complete failure in all language tasks in the initial period of right hemisphere anesthetization and a dysphasic period afterward; in left hemisphere anesthetization there should be no language deficits. When taking their lateralization index quotients into account, they said that a quotient of -0.85 to -1 is right-dominant (RD).

<u>Strongly bilateral</u>: "All nonright-nonleft-dominant patients would then be classified as 'bilateral.'" When taking their lateralization index quotients into account, they said that a quotient of 0.5 to -0.5 corresponds with strongly bilateral.

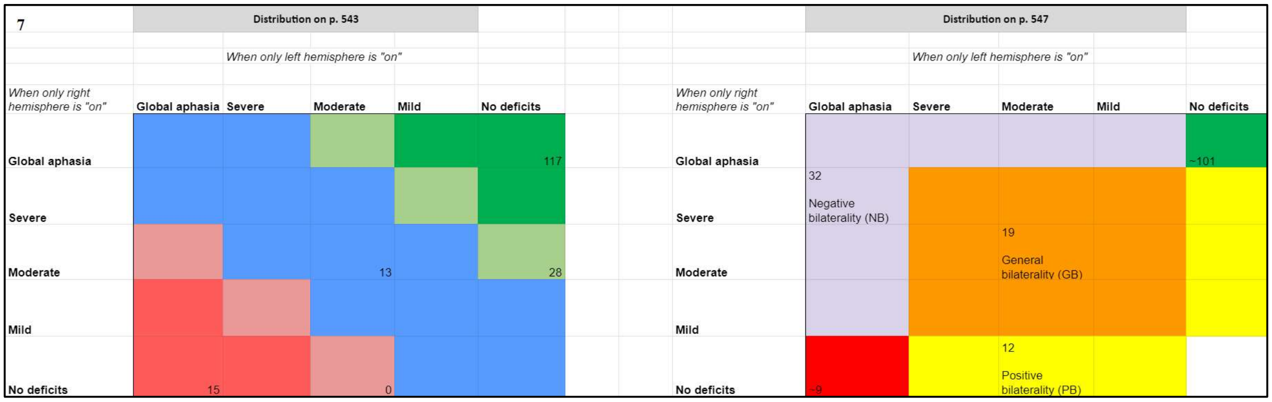
<u>Incomplete left-hemisphere dominance (ILD)</u>: When taking their lateralization index quotients into account, they said that a quotient of 0.85 to 0.5 is ILD. Relatedly, -0.5 to -0.85 would have been incomplete right hemisphere dominance, IRD, but that pattern "doesn't appear at all" (p. 543). The researchers also describe three kinds of bilaterality: "General bilaterality (GB) as indicated by an incomplete loss of language function in both IAPs, negative bilaterality (NB) as

indicated by an incomplete loss in one IAP and a complete loss in the other, and positive bilaterality (PB) with incomplete loss in one IAP and lack of language impairments in the other."

Distribution source: p. 543 lists the distribution for all of the patients, and p. 547 lists the distribution for the 63 patients that had LIs other than 1 or -1 (refered to as "B Patients"), and were categorized as having "positive bilaterality," "negative bilaterality," or "general bilaterality."

Matrix composition rationale: We used MATLAB to plot the LI equation that the researchers list. The matrix on the right was composed based on the researchers' brief description of positive bilaterality, negative bilaterality, and general bilaterality, in the second paragraph on p. 547. The researchers describe general bilaterality as an incomplete loss of language in both hemispheres, and we decided that "incomplete loss of language" was best translated into our categories of "Mild Deficits," "Moderate Deficits," and "Severe Deficits." Thus, the general bilaterality area is where the columns and rows for those categories intersect. Positive bilaterality is defined as incomplete loss of language in one IAP and no impairments in the other, so positive bilaterality occupies the two spaces in which the "No Deficits" column intersects with the "Mild Deficits," "Moderate Deficits," and "Severe Deficits" rows, and the "No Deficits" row intersects with the "Mild Deficits," "Moderate Deficits," and "Severe Deficits" columns. The researchers define negative bilaterality as an incomplete loss of language in one IAP and a complete loss in the other, and we decided that the phrase "complete loss" clearly translates into our category of "Global Aphasia." Thus, the negative bilaterality category occupies the space in which the "Global Aphasia" column intersects with the "Mild Deficits," "Moderate Deficits," and "Severe Deficits" rows, and the "Global Aphasia" row intersects with the "Mild Deficits," "Moderate Deficits," and "Severe Deficits" columns. Finally, the categories of right-hemisphere dominant and left-hemisphere dominant were tentatively added to the matrix, and placed in the only remaining cell which made sense for each, respectively: right-hemisphere dominant in the far left, bottom cell, and left-hemisphere dominant in the far right, top cell. The cell in which the "No

Deficits" row and column intersect was not accounted for by any of the category descriptions, so it was left blank.



8. **Article**: Objective criteria for reporting language dominance by intracarotid amobarbital procedure

Authors: Benbadis, S. R., Dinner, D. S., Chelune, G. J., Piedmonte, M., & Luders, H. O.

Handedness:

Right-handed: 139

Left-handed: 24

Ambidextrous: 2

Qualifying condition: All patients had medically intractable epilepsy and were being evaluated for epilepsy surgery.

Radiological evidence of brain lesion: p. 683, top left paragraph. A structural lesion, other than mesial temporal sclerosis, was present in 54 patients (33%).

Lateralization categories source: p. 683. The researchers explain that they "classified language lateralization as left, right, or bilateral (L, R, B) by three different methods, all based on the duration of speech arrest following the injection." Their three methods were as follows: (1)

Absolute duration of speech arrest, with cutoff of 60 s; (2) Side-to-side difference, with a cutoff of 30 s; (3) A "laterality index" defined as (L-R/L+R), with a cutoff of 0.5 s.

Distribution source: p. 685, in Table 1. We referred to the numbers in the "Total" row in Table 1, which shows the distribution as determined by two out of three methods. Left hemisphere language dominance: 126; right hemisphere language dominance: 20; and bilateral language dominance: 19.

Matrix composition rationale: We decided to use the same matrix configuration as that of Moddel et al. (2009). For the Moddel et al. (2009) matrix, we used MATLAB to code those three conditions. We mirrored the basic construction of the MATLAB plot on the matrix, but we decided that speech arrest from 20 seconds to 1 minute would potentially constitute a moderate deficit (i.e., we decided that it could represent anywhere from no deficit to a moderate deficit). Supposedly, it's normal for a patient to have a 20 second period of speech arrest, even if their language abilities are present in the tested hemisphere. We distinguished between bilateral dependent and bilateral independent in the earlier papers, but we merged them here. Note: The researchers discuss a second distribution in the paper—the distribution for which patient's classification did not differ at all across the three methods. We decided to not make a matrix for that distribution because the three out of three method is not what the researchers focus on; the first method, for which we built a matrix, is the paper's primary classification method.

Distribution of all pts as determined by two out of three methods (p. 685)					
8	*When only left hemisphere is "on"*				
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					126
Severe					
Moderate			19		
Mild					
No deficits	20				

9. **Article**: Sex differences in cerebral language dominance in complex-partial epilepsy

   Authors: Kurthen, M., Helmstaedter, C., Elger, C. E., & Linke, D. B.

   Note: No matrix could be built for this article and its distribution information was not included in the quantitative analysis.

10. **Article**: A reconsideration of bilateral language representation based on the intracarotid amobarbital procedure

    Authors: Risse, G. L., Gates, J. R., & Fangman, M. C.

    Handedness:

    Right-handed: 391

    Non-right-handed: 88

    The researchers state that "most patients classified as non-right-handed were left-handed, but a few were ambidextrous." They do not provide any further breakdown.

    Qualifying condition: Chronic epilepsy. Many of the patients "were believed to have" static atrophic lesions dating from early in life. For the patients who had a language classification, 126 had onset of seizures at five years or younger, and 160 had onset of seizures after the age of 10

(Figure 1). Note: This does not total to the number of patients who had language classification. Our guess is that this is because some patients had onset between these two points or unknown onset.

Radiological evidence of brain lesion: p. 122. The researchers state, "for many patients, there was evidence of structural brain damage that predated onset of seizures." However, no radiological information is listed or discussed.

Lateralization categories source: pp. 122–123. Language testing consisted of four "modalities of language processing" (rote/automatic speech, confrontation naming, simple reading, and auditory comprehension), which each contained multiple tasks. Each language task had different rules for the way points were assigned. Sometimes one point was given for each correct response and none for paraphasic errors; other times two points were given for each correct response and one for paraphasic errors, etc. The researchers explain that, "within each modality, raw scores were converted to a percent correct." Classification decisions were based on at least a 50% sampling of the total language items possible. Below are the criteria for each classification: Left-hemisphere dominance: Score higher than zero for each language modality after right-hemisphere injection, and global aphasia (i.e., failure on every language task), persisting until the time of motor recovery, after left-hemisphere injection. Right-hemisphere dominance: Score higher than zero for each language modality after left-hemisphere injection, and global aphasia (i.e., failure on every language task), persisting until the time of motor recovery, after right-hemisphere injection. Bilateral dominance: Score higher than zero for at least one language modality following both the right-hemisphere and left-hemisphere injection. Unclassified dominance: Any patient who failed to meet the criteria for one of the categories above (i.e., left-hemisphere dominance, right-hemisphere dominance, bilateral). This includes patients who demonstrated early return of motor function, prolonged obtundation following an injection, or prolonged speech arrest after both injections.

Distribution source: Table 1 on p. 124, Table 3 on p. 127, and pp. 127–128. The distribution figures were obtained by converting the percentages of *n* in each column (i.e., "Left," "Right," and "Bilateral") into numbers, and then adding the two rows in each column together. Left-hemisphere dominance = 304.16; right-hemisphere dominance = 23.68; and bilateral dominance = 40.16. These figures add to *n*, which is 368. We also accounted for the fact that the researchers likely rounded to get their percentages. If this were the case, there would be 39 bilateral patients. However, we found that no number rounded to the percentage listed for left hemisphere dominance and right hemisphere dominance.

Note: In Table 3, the *n* for each bilateral group adds to 28 (rather that 40.16, as indicated above). On p. 128, the researchers state that "the remaining 11 patients did not fit into any of the patterns identified." This suggests that the total *n* for the bilateral category is 39, rather than 40.16. This is a contradiction within the researchers' presented data.

Matrix composition rationale: Since a patient was only required to get a score higher than zero within each of the four language modalities (i.e., a single correct response when each modality is being tested) during right IAT to qualify as left-hemisphere dominant, we decided that it's plausible that the patient could still be mildly to moderately impaired when the left-hemisphere was acting alone. Thus, the left-hemisphere dominant area on the matrix includes the "No Deficits," "Mild Deficits," and "Moderate Deficits" columns. It includes only the "Global Aphasia" row for the right-hemisphere, because another requirement for a patient to qualify as left-hemisphere dominant was that they demonstrate global aphasia when the right hemisphere was acting alone. The right-hemisphere dominant area on the matrix is then the complete reverse of this. Regarding the researchers' general definition of bilaterality, in order for a patient to be classified as having bilateral dominance, they simply had to obtain a score higher than zero (i.e., a single correct response when one modality was being tested) for both injections. The researchers do not specify whether there needed to be symmetry here (i.e., whether the patient needed to obtain a score higher than zero for *the same* modality on each injection). Thus, we decided that a patient could have experienced no deficits, or mild to severe deficits for each of the injections, and that the presence/degree of deficits could differ for the two hemispheres. This is why the bilateral dominance cells extend from "No Deficits" to "Severe Deficits" in both the columns and rows. The researchers did not specify that a patient *must* make some kind of error in order to qualify as having bilateral dominance, so the cell in which the "No Deficits" row and column converge is included in the bilateral area. Finally, as the unclassified dominance category was simply defined as cases in which a patient failed to meet the criteria for one of the other categories, it occupies the remaining three cells. With regard to the subgroups within the bilateral group, we examined the percentage correct for each of the four speech tasks (i.e., automatic speech, naming, comprehension, and reading) when the right hemisphere and left hemisphere were acting independently. This is detailed in Table 3, on p. 127. Our choices about which cells the subgroups should occupy on the matrix were based on the following observations:

Group I: The percentage correct for the left hemisphere was consistently high across tasks, and the percentage correct for the right hemisphere was consistently low across tasks. The only reason this group was not categorized as being left-hemisphere dominant was that the right hemisphere obtained a percentage score higher than 0% for one of the tasks. The only ability that the right hemisphere has, acting alone, is partial automatic speech.

Group II: The only difference between this group and Group I is that the right hemisphere of these patients has partial comprehension abilities.

Group III: In this group, when the right hemisphere was acting alone, it's possible that there was a patient who had perfect performance (i.e., no deficits at all). However, when the left hemisphere was acting alone, the patients exhibited severe deficits.

Group IV: In this group, patients exhibited very mild deficits when both the right hemisphere was acting alone and when the left hemisphere was acting alone. Regarding the remaining 11 patients, first mentions in the fourth paragraph on p. 127, the researchers state: "The remaining 11 patients did not fit into any of the patterns identified. Ten of these patients demonstrated some automatic speech in the right hemisphere in combination with either reading, naming, or auditory comprehension. One patient showed some reading ability only in the right hemisphere." (p. 128) So, these patients each scored higher than zero in *two* of the language modality tasks, in contrast to the four that would be required to establish hemispheric dominance. We know that these patients have two modalities at least partially intact, but the researchers do not specify how intact. We also cannot assume that the left hemisphere has no deficits, because in the four subgroups previously described, the left hemisphere always shows some deficits on at least one of the tasks. Thus, these 11 patients were added to the area on the matrix for Group I and Group II.

10		*When only left hemisphere is "on"*			
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia	"unclassified"				304.16
Severe			30	Group I and Group II, and the remaining 11 bilateral pts	
Moderate		Group III			
Mild		7		Group IV	
No deficits	23.68				2

11. **Article**: Patterns of language dominance in focal left and right hemisphere epilepsies: Relation to MRI findings, EEG, sex, and age at onset of epilepsy

    Authors: Helmstaedter, C., Kurthen, M., Linke, D. B., & Elger, C. E.

    Handedness:

    Right-handed: 137

    Left-handed: 24

    Ambidextrous: 6

Qualifying condition: Patients all had focal epilepsies who were candidates for surgical treatment of epilepsy.

Radiological evidence of brain lesion: p. 137 and pp. 143–144. The researchers state that "postoperative histology revealed tumors (50%), malformations (25%), atrophy (13%), vascular disorders (6%), and other lesions (6% hematoma, abscesses, necroses, etc.) in the group of patients with lesions found by imaging techniques." They also state that: "With regard to radiological localization of lesions, 40% of all patients had lesions within the temporal region, 20% had extratemporal and/or extensive lesions. In 40% of all patients, no structural lesions could be detected by MRI and/or CCT."

Lateralization categories source: p. 138, in the #7 section. The researchers use an LI to categorize patients into their respective lateralization categories. Their LI equation is L = [(ScoreIAPRight - Score IAPLeft) / (ScoreIAPRight + ScoreIAPLeft)] x (n/m). Their LI ranges are: above 0.79 for left-hemisphere dominance; between 0.8 and 0.3 for incomplete left hemisphere dominance; between 0.29 and -0.29 for bilateral dominance; between -0.3 and -0.7 for incomplete right hemisphere dominance; and below -0.79 for right hemisphere dominance. We expanded on this to facilitate matrix building: There were 7 tasks. Two points were given for a faultless performance of each task, one point for an impaired performance, and no point for a complete failure. Thus, the total score for each IAP ranged between 0 and 14. From that score, a lateralization index was computed.

<u>Left-hemisphere dominance</u>: A lateralization index quotient of above 0.79. "Complete" left-hemisphere dominance is 1.

<u>Incomplete left-hemisphere dominance</u>: A lateralization index quotient between 0.8 and 0.3.

<u>Right-hemisphere dominance</u>: A lateralization index quotient of less than -0.79. "Complete" right-hemisphere dominance is -1.

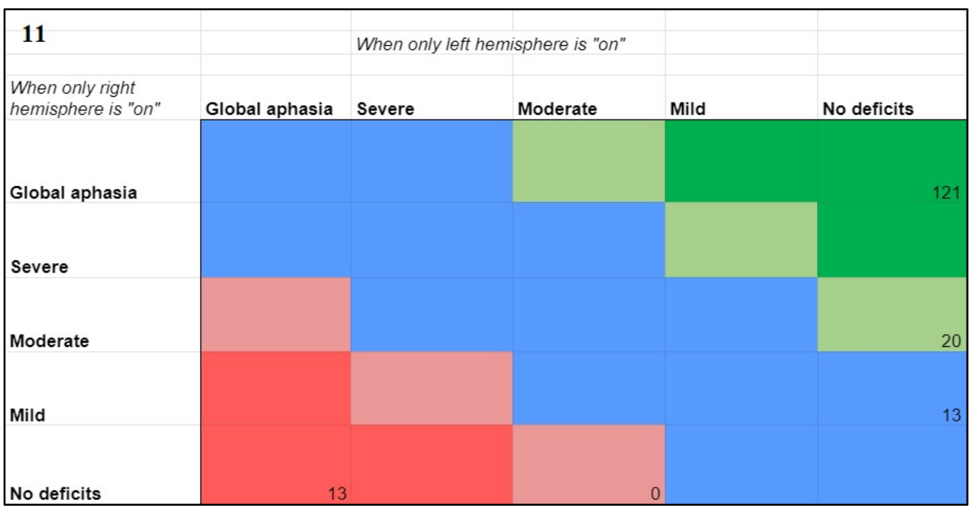
<u>Incomplete right-hemisphere dominance</u>: A lateralization index quotient of -0.3 and -0.7. Note: No patients fell into this category.

Bilateral dominance: A lateralization index quotient between 0.29 and -0.29.

Distribution source: p. 140, in Figure 2. We added the "LHE" (left hemisphere epilepsy) and "RHE" (right hemisphere epilepsy) rows for each of the lateralization category bars in Figure 2. Right hemisphere dominance: 13; bilateral dominance: 13; incomplete left hemisphere dominance: 20; left hemisphere dominance: 121.

Note: the researchers had an incomplete right hemisphere dominance category, but none of the patients fell into that category, so it was left out of Table 2.

Matrix composition rationale: We used MATLAB to plot the LI equation that the researchers list.



12. **Article**: Effects of anomalous language representation on neuropsychological performance in temporal lobe epilepsy

Authors: Loring, D. W., Strauss, E., Hermann, B. P., Perrine, K., Trenerry, M. R., Barr, W. B., Westerveld, M., Chelune, G. J., Lee, G. P., & Meador, K. J.

Handedness:

Right-handed: 469

Non-right-handed: 82

Note: Calculated from Table 1

Qualifying condition: All patients had complex partial seizures of left temporal origin and underwent Wada as part of their preoperative evaluation for possible epilepsy surgery.

Radiological evidence of brain lesion: 164 patients had brain lesions. The researchers do not describe the nature of the brain lesions: "The effect of the presence of a structural lesion could not be properly investigated because of a small sample size and because structural lesions were coded in the database only as being present or absent." (This was found in the discussion section).

Lateralization categories source: Article did not include an explanation of how patients were organized into lateralization categories. The researchers pulled patients from the Bozeman Epilepy Consortium, a neuropsychology database to which nine different epilepsy surgery centers contribute. Thus, they do not list how the medical teams at those centers made their lateralization decisions, and indeed, those teams may have assigned patients to lateralization categories based on different principles.

Distribution source: Article did not have page numbers. Distribution was listed in the "Methods" section, at the end of the second paragraph. Left: 455; Right: 48; Bilateral: 58.

Matrix composition rationale: No matrix could be built.

Note: No matrix could be built for this article, but its distribution information was included in the quantitative analysis.

13. **Article**: Epileptic activity influences the speech organization in medial temporal lobe epilepsy

    Authors: Janszky, J., Jokeit, H., Heinemann, D., Schulz, R., Woermann, F. G., & Ebner A.

    Handedness:

    Right-handed: 83

    Left-handed: 17

    Note: Figures calculated from first paragraph of results section on p. 2045.

Qualifying condition: Medial temporal lobe epilepsy due to unilateral hippocampal sclerosis, but lacking other epileptogenic lesions.

Radiological evidence of brain lesion: Yes. The researchers state that: “(i) all patients had left-sided brain injury and epilepsy” and “(iii) no patient had a lesion in the brain regions responsible for the speech production” (p. 2048).

Lateralization categories source: p. 2045, in the "Wada test procedure" section. However, their explanation is incomplete. While they say how points were calculated and that 104 points for a single IAT indicated "complete unimpaired speech production of the investigated hemisphere," they do not discuss how decisions were made when impairment was present and the full 104 points was not attained.

Distribution source: Calculated from the Wada test procedure section on p. 2045, in which the researchers state that there were "100 patients, 17 of whom has right-sided MTLE," coupled with the statement in the results section that "of 100 patients in whom the Wada test was performed, left-sided speech occurred in 75.9% of the left-sided and in 100% of the right-sided MTLE." Thus, there were 83 left-sided MTLE patients and 17 right-sided MTLE patients. So, 80 of the total 100 patients had left-hemisphere dominance. The others fell into the atypical dominant category (i.e., right or bilateral). The article does not report individual distribution numbers for the right-hemisphere dominant and bilateral categories.

Note: This article does define "atypical" as right or bilateral in their abstract.

Matrix composition rationale: No matrix could be built for this article.

Note: No matrix could be built for this article, but its distribution information was included in the quantitative analysis.

14. **Article**: Language lateralization by Wada test and fMRI in 100 patients with epilepsy

    Authors: Woermann, F. G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., Okujava, M., Wolf, P., Tuxhorn, I., & Ebner, A.

Handedness:

Right-handed: 80

Left-handed: 20

Qualifying condition: p. 699. All patients had localization-related epilepsy. The specific breakdown is as follows: 63 had left-sided TLE, 19 had left-sided extratemporal epilepsy (including multilobar epilepsy), 11 had right-sided TLE, and 7 had right-sided extratemporal epilepsy.

Radiological evidence of brain lesion: Not addressed.

Lateralization categories source: p. 699, in the "Methods" section. All that is said about determining lateralization categories from Wada is the following: "Studies were performed following injection of 150 mg of amobarbital and yielded instantaneous results of typical, that is, left-sided dominance for language, or atypical, that is, right-sided or bilateral representation." The article points to supplementary information available on neurology.org. In that supplementary document, the researchers defined their lateralization categories as follows: "Language lateralization was based on evaluation of a patient's performance in receptive and expressive language tasks. Speech arrest, comprehension, word finding and naming difficulties, difficulties with repetition, neologisms, and paraphasias were used to essentially classify the temporary aphasia as global, non-fluent, or fluent. Marked language impairment with left sided injection and minimal or no impairment after right sided injection was categorized as left hemisphere language dominance (coined "typical" in our study). Marked language impairment with right sided injection and minimal or no impairment after left sided injection was judged right hemisphere language dominance (coined "atypical" in our study). Marked language impairment with both injections meant bilateral language dominance (coined "atypical" in our study)." (p. 1)

Distribution source: p. 699, in the first sentences of the "Results" section, and p. 700, in the column heads of Table 1. Typical lateralization = 71; atypical lateralization = 29. The researchers do not report figures for the subcategories of the "atypical category" (i.e., right hemisphere dominance and bilateral dominance). They offer an explanation for this on p. 2 of their supplementary information document: "Pragmatically categorizing patients with right sided and bilateral dominance to one 'atypical' group follows Wyllie's notion: '…, we believe that patients with right or bilateral dominance on Wada testing should have cortical stimulation for localization of language areas if extensive left or right temporal or frontal resection is planned.'"

Matrix composition rationale: We decided that the researchers' definition of left-hemisphere dominance as "marked language impairment with left sided injection and minimal or no impairment after right sided injection" best translates into "Moderate Deficits" to "Global Aphasia" when the right hemisphere is acting alone and "No Deficits" to "Mild Deficits" when the left hemisphere is acting alone. (We chose to represent the researchers' term "marked" as anything ranging from moderate deficits to global aphasia, reasoning that the term "marked" was likely inconsistent with mild deficits. If mild deficits were meant to be included in this category, the researchers could have simply said "any impairment" rather than "marked impairment"). Since the researchers defined right-hemisphere dominance as "marked language impairment with right sided injection and minimal or no impairment after left sided injection," right-hemisphere dominance translated into the reverse of that of left-hemisphere dominance. Finally, as the researchers defined bilateral language dominance as "marked language impairment with both injections," and we had decided to represent "marked" as anything from "Moderate Deficits" to "Global Aphasia," bilateral language dominance translates into the cells for which the "Moderate Deficits" and "Global Aphasia" columns and rows converge.

Note: Since the researchers do not report separate figures for right-hemisphere dominance and bilateral dominance, those two categories will be collapsed into a single "atypical lateralization" category on the matrix.

14					
		When only left hemisphere is "on"			
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					71
Severe					
Moderate			29 (atypical count)		
Mild					
No deficits					

15. **Article**: Atypical speech is rare in individuals with normal developmental histories

    Authors: Miller, J. W., Dodrill, C. B., Born, D. E., & Ojemann, G. A.

    Handedness:

    Right-handed: 47

    Left-handed: 3

    Found on p. 1043, in Table. Note that handedness is only reported for the group of 50 patients that met the criteria described below.

    Qualifying condition: p. 1043, in "Patients and methods" section. For the group of 50 patients (represented by the matrix on the left), all patients met the following criteria: 1) Normal neurological history through the age of 15 years; 2) Definite head injury or cerebral infection (meningitis, encephalitis) after age 15 years as presumed cause of epilepsy; and 3) Onset of epilepsy after the head injury or infection. There were 786 patients who did not meet these criteria, and lateralization is also reported for them.

    Radiological evidence of brain lesion: The radiological histories of the group of 786 patients is not stated. It is possible that they did not have normal neurological histories through the age of 15 years, and it is possible that they did but then did not later have a head injury or cerebral infection. It is also possible that they had a normal neurological history through the age of 15, later had a head injury or cerebral infection, but then did not develop epilepsy following the injury or infection. However, for the group of 50 patients, the researchers state that 38 had a head trauma and 12 had a cerebral infection. No radiological information is provided.

Lateralization categories source: p. 1043, in the third paragraph of the "Patients and methods" section. The researchers state: "Ability to generate speech (Table 2) was determined from speech blockage, dysphasia, or both (especially object naming errors) as follows: 1) Left (typical) speech—with the left injection only; 2) Right (atypical) speech—with the right injection only; 3) Bilateral (atypical) speech—with both injections."

Distribution source: p. 1043, in Table 2. We obtained the distribution figures for the full set of 836 patients by adding the numbers in the columns for "Left (typical) speech," "Right (atypical) speech," and "Bilateral (atypical) speech."

<u>The 50 patients with normal neurological histories</u>: Left-hemisphere dominance = 50 Right-hemisphere dominance = 0 Bilateral dominance = 0

<u>The 786 patients without normal neurological histories or who did not have infarct leading to epilepsy after age 15</u>: Left-hemisphere dominance = 664 Right-hemisphere dominance = 66 Bilateral dominance = 56

<u>All 836 patients</u>: Left-hemisphere dominance = 714 Right-hemisphere dominance = 66 Bilateral dominance = 56

Matrix composition rationale: The researchers define left-hemisphere dominance as "speech blockage, dysphasia, or both (especially object naming errors)" with left injection only, right hemisphere dominance as those impairments with right injection only, and bilateral dominance as those impairments with both injections. The researchers do not specify what degree of those behaviors must be present, so we made the assumption that they could range anywhere from mild to extreme and thus translated into "Mild Deficits" to "Global Aphasia" on the matrix. So, left-hemisphere dominance translates into "Mild Deficits" to "Global Aphasia" when the right hemisphere is acting alone and "No Deficits" when the left hemisphere is acting alone. Right-hemisphere dominance is the reverse of this. Bilateral dominance translates into the cells for which the "Mid Deficits" to "Global Aphasia" columns and rows converge.

15

	The 50 pts with normal neurological histories				
	When only left hemisphere is "on"				
When only right hemisphere is "on"	Global aphasia	Severe	Moderate	Mild	No deficits
Global aphasia					50
Severe					
Moderate			0		
Mild					
No deficits	0				

	The 786 pts *without* normal neurological histories or who didn't have infarct leading to epilepsy after age 15				
	When only left hemisphere is "on"				
When only right hemisphere is "on"	Global aphasia	Severe	Moderate	Mild	No deficits
Global aphasia					664
Severe					
Moderate			56		
Mild					
No deficits	66				

	All 836 pts together				
	When only left hemisphere is "on"				
When only right hemisphere is "on"	Global aphasia	Severe	Moderate	Mild	No deficits
Global aphasia					714
Severe					
Moderate			56		
Mild					
No deficits	66				

16. **Article**: Lateralising value of neuropsychological protocols for presurgical assessment of temporal lobe epilepsy

Authors: Akanuma, N., Alarcón, G., Lum, F., Kissani, N., Koutroumanidis, M., Adachi, N., Binnie, C. D., Polkey, C. E., & Morris, R. G.

Handedness:

Right-handed: 98

Non-right-handed: 27

Note: Calculated from Table 1 by adding the numbers before the dash and the numbers after the dash in the "Handedness" row.

Qualifying condition: Patients qualified for the study based on the following criteria: "(a) patients underwent TL for the treatment of their partial epilepsy at the Maudsley or King's College Hospitals (London) between 1987 and 2000; (b) presurgical assessment included a standard battery of noninvasive neuropsychological tests and the Wada test; (c) patients were older than 16 years at the time of presurgical assessment; (d) English was the patient's first language; and (e) full-scale intelligence quotient (FSIQ) was >70." (p. 409)

Radiological evidence of brain lesion: Not addressed.

Lateralization categories source: p. 410, in the second paragraph of the "Wada test" section. Note: "We combined right and mixed speech dominant patients together into a non-left speech group, because the smaller number of patients in these groups did not allow separate analyses."

Distribution source: p. 411, in Table 1

Matrix composition rationale: The researchers only make one statement about their laterality decisions, and it is the following: "Language dominance was assessed clinically on the basis of observation of positive signs of dysphasia and inability to read the words or name the line drawings presented." Thus, we assumed that any signs of dysphasia indicated that the patient was either dominant on the anesthetized hemisphere or had "mixed" (i.e., bilateral) dominance. So, the "No Deficits" for right hemisphere and left hemisphere cell is left blank, because in order to qualify as bilateral, the patient has to demonstrate dysphasia on at least one of the hemispheres.

16		*When only left hemisphere is "on"*			
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					98
Severe					
Moderate			27 (atypical count)		
Mild					
No deficits					

17. **Article**: The impact of sex and language dominance on material-specific memory before and after left temporal lobe surgery

    Authors: Helmstaedter, C., Brosch, T., Kurthen, M., & Elger, C. E.

    Handedness:

Right-handed: 138.77

Left-handed: 11.64

Ambidextrous: 18.59

Note: Calculated from Table 1 by multiplying the percentages for "Right," "Ambidextrous," and "Left" in the "Men" and "Women" columns by the *n* for men and women, and then adding the figures for each handedness row.

Qualifying condition: p. 1519. All patients had L-TLE and underwent epilepsy surgery for control of otherwise uncontrollable seizures.

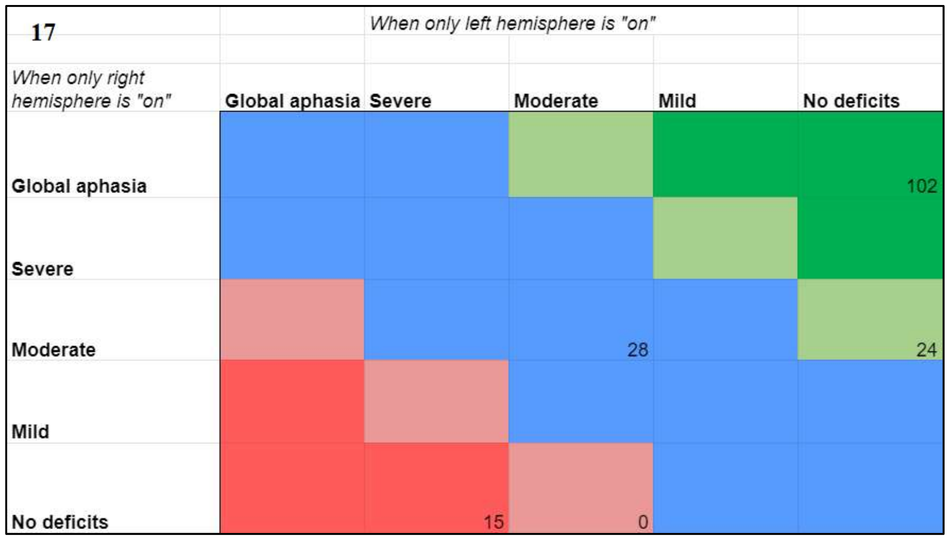
Radiological evidence of brain lesion: p. 1520, Table 1. By multiplying the percentages in the "Pathology" rows by the *n* for men and the *n* for women, and then adding the resulting figures across each "Pathology" row, the following distribution is found: 16.15 patients with no pathology finding; 57.85 patients with hippocampal sclerosis; 39.99 patients with tumor; 36.8 patients with developmental pathology; and 18.21 patients with other pathology.

Lateralization categories source: p. 1520, last two paragraphs on the left-hand side. LI equation is L = [(ScoreIAPRight - Score IAPLeft) / (ScoreIAPRight + ScoreIAPLeft)] x (n/m). The LI ranges are: above 0.8 for left-hemisphere dominance; 0.3 to 0.8 for incomplete left-hemisphere dominance; below 0.3 to "more than -0.3" for bilateral dominance; and below -0.8 for right-hemisphere dominance.

Note: There was no patient with incomplete right-hemisphere dominance.

Distribution source: p. 1521, calculated by adding the male and female counts for right-hemisphere dominance, incomplete left-hemisphere dominance, and bilateral dominance, and then subtracting the sum of all of those categories from *n* (*n* = 169) to get the left-hemisphere dominant figure. These numbers can be confirmed by adding the male and female counts in Table 2, on p. 1522.

Matrix composition rationale: We used MATLAB to plot the LI equation that the researchers list. (This is the same code and matrix configuration used for several other articles that employed a LI equation to determine lateralization categories).



18. **Article**: Magnetocephalography: a noninvasive alternative to the Wada procedure

Authors: Papanicolaou, A. C., Simos, P. G., Castillo, E. M., Breier, J. I., Sarkari, S., Pataraia, E., Billingsley, R. L., Buchanan, S., Wheless, J., Maggio, V., & Maggio, W. W.

Handedness:

Left-handed: 11

Right-handed: 89

Found in p. 868, in "Patient Population" section.

Qualifying condition: p. 868. All patients had intractable partial seizure disorder and were candidates for focal resection epilepsy surgery.

Radiological evidence of brain lesion: Not addressed.

Lateralization categories source: p. 869, in the last three sentences of top left paragraph.

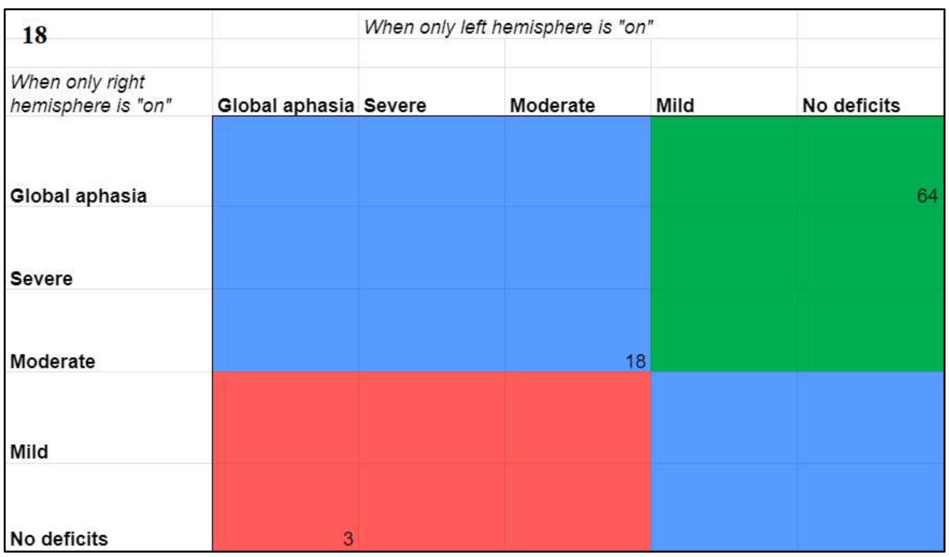
Laterality categories were in part determined from "signs like the interruption of expressive language (speech arrest or paraphasic production during naming, repetition, or reading) as well as receptive language performance (inability to produce accurate motor response to simple and complex commands)." The researchers explain that, "In general, a hemisphere was deemed to support language when its injection resulted in the disruption of language in at least two of the aforementioned tests, with either one test being rated as having at least moderate disruption or at least three of the four tests being characterized with at least mild disruption. Unilateral language representation was inferred when only one hemisphere met these criteria. Bilateral language representation was inferred when criteria were met either during injection of both hemispheres, or when neither hemisphere met criteria despite adequate amounts of injected barbiturate agents and in the absence of any evidence for anomalous vascularization."

Distribution source: p. 872, adding the Wada procedure columns for each of the laterality categories (i.e., "Lt," "Bilat," and "Rt").

Note: Even though n = 100 in this study, the distribution is only reported for the 85 patients who underwent both the Wada and MEG procedure. It's explained on p. 870 that "data from 15 patients were excluded from further analyses because they did not meet one or more of the criteria listed previously."

Matrix composition rationale: A hemisphere was determined to support language when a patient’s language was "disrupted" (i.e., "speech arrest or paraphasic production during naming, repetition, or reading…inability to produce accurate motor response to simple and complex commands," (top of p. 869) in at least two of their four tests, with either one test "being rated as having at least moderate disruption" or "at least three of the four tests being characterized with at least mild disruption." Further, a patient would be designated as right-hemisphere dominant or left-hemisphere when "only one hemisphere met these criteria." A patient was designated as having bilateral dominant when criteria was met for both hemispheres or neither hemisphere (p. 869). We decided that the group of patients who displayed mild disruption in 3/4 tasks *combined* with the group of patients who displayed moderate disruption of 1/4 tasks should be mapped as

"Moderate Deficits" on the matrix. Further, since the criteria for right-hemisphere or left-hemisphere dominant is displaying this combination of disruptions in only one hemisphere, the other hemisphere could have mild disruptions and still not cause the person to be classified as bilateral (e.g., the other hemisphere could have mild deficits in 3/4 tasks and simply be lacking the moderate deficits in one task). This why the right-hemisphere and left-hemisphere dominant matrix areas include both "No Deficits" and "Mild Deficits" for the dominant hemispheres. Regarding the bilateral area, as a bilateral patient potentially could have not met the unilateral criteria for either hemisphere, they could have mild deficits (e.g., only mild deficits on 1/4 tasks) on both of the IATs or no deficits on both of the IATs.



19. **Article**: Gender differences in handedness and speech lateralization related to early neurologic insults

    Authors: Miller, J. W., Jayadev, S., Dodrill, C. B., & Ojemann, G. A.

    Handedness:

    Left-handed: 36

    Right-handed: 134

Found on p. 1975, in the "Speech lateralization and handedness by gender" table.

Qualifying condition: p. 1974, at the top of the right-hand column. All patients had a history of a temporally well-defined insult from CNS infection (n = 87) or trauma (n = 83) as the likely cause of epilepsy without prior neurologic insult.

Radiological evidence of brain lesion: See above. Researchers state that a "detailed breakdown of handedness and speech lateralization by gender and age of neurologic insult is given" in Table E-1 on the *Neurology* website.

Lateralization categories source: p. 1974, in the second paragraph on the right-hand side. The researchers state that "atypical speech was defined as a speech disturbance with both injections, or only with injection on the right." These speech disturbances were supposedly noted during the only language task the researchers describe, which is as follows: "A repeating task (object naming, reading, recall of the object named) was begun at injection and continued until function completely returned."

Distribution source: Table on p. 1975. The figures are in the "Total" column, in the rows for "Typical Speech" and "Atypical Speech."

Matrix composition rationale: As the researchers do not specify how great or small a patient's speech errors had to be or could be to qualify as a "speech disturbance," we are assuming that *any* speech error, in the range from mild to global aphasia, was considered a "speech disturbance." Thus, a patient could have symmetrical errors (e.g., mild and mild) for both hemispheres and qualify as having bilateral dominance, or asymmetrical errors (e.g., mild and global aphasia) in their two hemispheres and qualify as having bilateral dominance. We are also assuming that when the researchers say "injection on the right" and explain that speech disturbances with injection on the right qualified a patient as having atypical language dominance, they are referring to the right *hemisphere* (i.e., the condition in which the left hemisphere was acting alone) and not the right femoral artery. In accordance with the researcher's definitions, a patient could have deficits ranging from mild to global aphasia when the left hemisphere was acting alone and qualify as having right-hemisphere dominance, if they then had no deficits when the right hemisphere was acting alone.

Note: The "No Deficits" for both hemispheres cell is not designated bilateral because the researchers define bilateral dominance as speech disturbance with both IAPs, and while the researchers never explicitly define left-hemisphere dominance (thus leaving the possibility that no speech disturbance in both IAPs could qualify a patient as being left-hemisphere dominant), we decided that this was too inconsistent with the reasoning displayed in the definitions the researchers *did* provide. In other words, it makes sense that the researchers would define left-hemisphere dominance as speech disturbances only when the right hemisphere was acting alone, as they imply that right-hemisphere dominance is speech disturbances only when the left hemisphere was acting alone.

19	*When only left hemisphere is "on"*				
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					
Severe					
Moderate			24		
Mild					146
No deficits					

20. **Article**: Degree of handedness and cerebral dominance

Authors: Isaacs, K. L., Barr, W. B., Nelson, P. K., & Devinsky, O.

Handedness:

Strong left: 16

Moderate left: 11

Ambidextrous: 11

Moderate right: 38

Strong right: 98

Qualifying condition: Epilepsy surgery candidates.

Radiological evidence of brain lesion: Not reported.

Lateralization categories source: p. 1856, beginning at the last paragraph on the left-hand side. The researchers state that "Hemispheric representation of language functioning was dependent on the presence of speech arrest as well as pathognomic signs of paraphasias and dysnomia in excess of baseline functioning. Transient speech arrest with rapid and complete resumption of language functions was no considered sufficient for the determination of language representation in that hemisphere. Bilateral speech representation was identified when the patients were either bilaterally aphasic or bilaterally normal."

Distribution source: p. 1856, Table 2. Distribution was found by adding the numerators in the *n* row in order to obtain the number of left-hemisphere dominant patients, then subtracting the number of left-hemisphere dominant patients from 174 (*n* = 174) to get the number of atypical dominant patients. The number of left-hemisphere dominant patients was confirmed by subtracting the numerators from the denominators in the Table 2 *n* row and adding those figures. Note: The first sentence of the "Methods" section implies that *n* = 193, but *n* = 174 as per abstract and adding *n* for the "male" and "female" categories in Table 1 (the demographics table). The researchers do not explain why the 19 additional patients were not included in their demographics or analysis.

Matrix composition rationale: While the researchers state that speech arrest and paraphasias/dysnomia were used to determine laterality, and that temporary speech arrest did not factor into those determinations, they do not give further detail about the number of errors or severity of errors necessary for various determinations. However, they do give additional detail regarding the category of bilateral dominance. They state that "bilateral speech representation was identified when the patients were either bilaterally aphasic or bilaterally normal." Thus, the cells for the range of "Mild" through "Global Aphasia" (as the researchers do not specify a severity of aphasia) for both hemispheres are designated as bilateral (i.e., cells for which both hemispheres are somewhere in that range), and the "No Deficits" for both hemispheres cell is designated as bilateral. The right-hemisphere dominance and left-hemisphere dominance cells are the cells that remain after accounting for the bilateral category. We made the assumption, for the left-hemisphere dominance and right-hemisphere dominance categories, that the contralateral hemisphere could display deficits ranging from mild to global aphasia, because those possibilities were not accounted for in the bilateral category. For example, the researchers did not say that full abilities in one hemisphere and merely mild deficits in the other would qualify a patient as bilateral.

Note: We are defining the "as well as" as an "or" in the following sentence: "the presence of speech arrest as well as pathognomic signs of paraphasias and dysnomia in excess of baseline functioning."

20		*When only left hemisphere is "on"*			
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					
Severe					
Moderate			133		
Mild					41
No deficits					

21. **Article**: Expressive and receptive language areas determined by a non-invasive reliable method using functional magnetic resonance imaging and magnetoencephalography

    Authors: Kamada, K., Sawamura, Y., Takeuchi, F., Kuriki, S., Kawai, K., Morita, A., & Todo, T.

    Note: No matrix could be built for this article and its distribution information was not included in the quantitative analysis.

22. **Article**: Unexpected right hemisphere language representation identified by the intracarotid amobarbital procedure in right-handed epilepsy surgery candidates

    Authors: Cunningham, J. M., Morris III, G. L., Drea, L. A., & Kroll, J. L.

    Handedness:

    Right-handed: 122

    Left-handed: 29

    Ambidextrous: 5

    Qualifying condition: Epilepsy surgery candidates.

    Radiological evidence of brain lesion: Not reported.

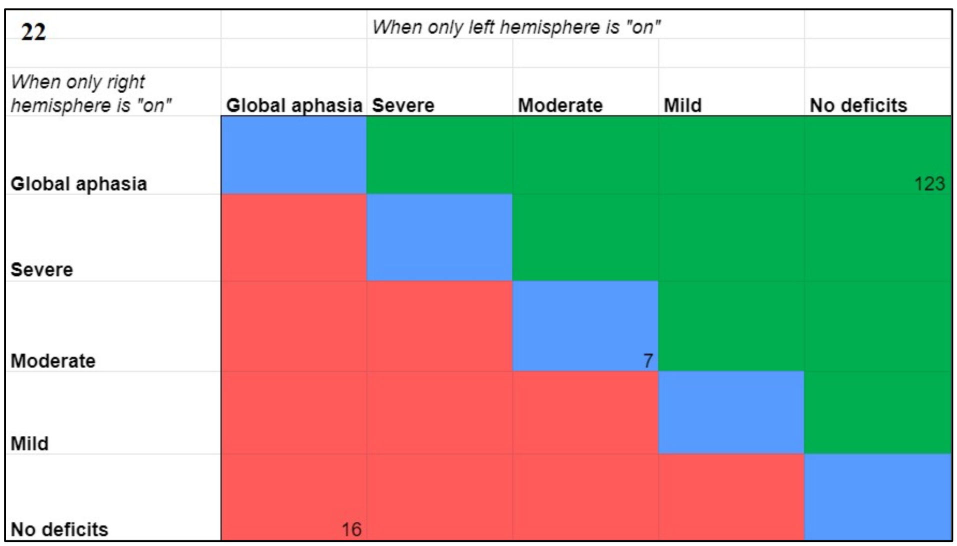
    Lateralization categories source: p. 140, in the "2.3. Lateralization index" section. On each IAP, items were scored individually, and the patient could receive a maximum total score of 33 for the IAP if every item was given. The researchers then explain: "The right hemisphere language score (RLS) and left hemisphere score (LLS) represent percentages that were computed by dividing the total correct by the total number possible for that hemisphere and then multiplying by 100. (For example, if 24 total items were administered to the left hemisphere and the patient received 12 points, then the LLS would be 50). The RLS was then subtracted from the LLS to produce a lateralization index (LI) ranging from +100 to -100, where positive scores indicate left hemisphere language dominance and negative scores indicate right hemisphere language dominance. For the purpose of this study, *language representation* refers to the finding of any score greater than 0 in either hemisphere. [...] *language dominance* refers to any LI greater than

+15 or less than -15." On p. 141, below Table 4, the researchers clarify that "left dominant LI > +15; right dominant LI < -15."

Distribution source: p. 141, Table 4, in the bottommost "Totals" row for the columns "Left," "Mixed," and "Right." Left = 123; Mixed = 7; Right = 16.

Note: This distribution adds to 146, and n = 156 in the study. Moreover, the first sentence of the last paragraph on p. 141 confirms that all 156 patients received IAPs. So, we are making the assumption that 10 patients were nondiagnostic, but the researchers never explicitly state this.

Matrix composition rationale: We used MATLAB to plot the LI equation that the researchers list.



23. **Article:** Extent of initial injury determines language lateralization in mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS)

Authors: Rathore, C., George, A., Kesavadas, C., Sarma, P. S., & Radhakrishnan, K.

Handedness:

Right-handed: 120

Left-handed: 4

Qualifying condition: All patients had left mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) and had undergone resection.

Radiological evidence of brain lesion: Yes. The researchers state: “HS was defined as presence of unequivocal atrophy of the hippocampus with corresponding increase in the signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Patients with additional extratemporal abnormalities on MRI were included in this study if their seizures were considered to be of mesial temporal origin.” (p. 2250). Also, extratemporal MRI changes are listed in Table 1 and Table 2.

Lateralization categories source: p. 2251, in the last four sentences of the paragraph on the upper left-hand side. The potential scores a patient could receive on the language items added to 16. The researchers explain: "Language dominance was determined and patients were classified as left, right, or codominant for language according to the scores obtained for each of the hemispheres on the 16-point scale. A score of <8 on ipsilateral injection and >13 on the contralateral injection was taken to signify the presence of aphasia on the ipsilateral side, indicating that the injected hemisphere was dominant for language. These scores were chosen, although arbitrarily, to represent a value of less than 50% and more than 80%, respectively. All other combinations were classified as co-dominance." Note: This study technically includes 148 patients —124 with left MTLE and 24 with right MTLE. But the study focuses on the 124 left MTLE patients, and only reports a percentage of atypical dominance for the 24 right MTLE patients. For the 124 left MTLE patients, the researchers provide a full distribution (i.e., with the right-hemisphere dominance figures and the bilateral figures).

Distribution source: p. 2251, in the "Subject characteristics" section for the right MTLE patients and in the "Prevalence of ALL among patients with left MTLE-HS" section for the left MTLE patients. Right MTLE patients: 4.1% had atypical dominance and there were 24 in total, so 0.984 patients (i.e., 1 patients) had atypical dominance and 23 patients had left-hemisphere dominance.

Left MTLE patients: 15 had right-hemisphere dominance; 8 had bilateral dominance; 101 had left-hemisphere dominance.

Matrix composition rationale: We decided that a score of below 8 translates to mild deficits or no deficits. We decided that a score of above 13 translates to moderate deficits through global aphasia. The researchers did not define bilaterality.

Note: We decided to only plot the distribution for the left MTLE patients because the right MTLE patient group had an *n* below 100.

23	Left MTLE pts				
		When only left hemisphere is "on"			
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					101
Severe			8		
Moderate					
Mild					
No deficits			15		

24. **Article**: Atypical language lateralization in epilepsy patients

    Authors: Möddel, G., Lineweaver, T., Schuele, S. U., Reinholz, J., & Loddenkemper T.

    Handedness:

    Right-handed: 391

    Left-handed or ambidextrous: 54

    Found on p. 1508, in Table 2.

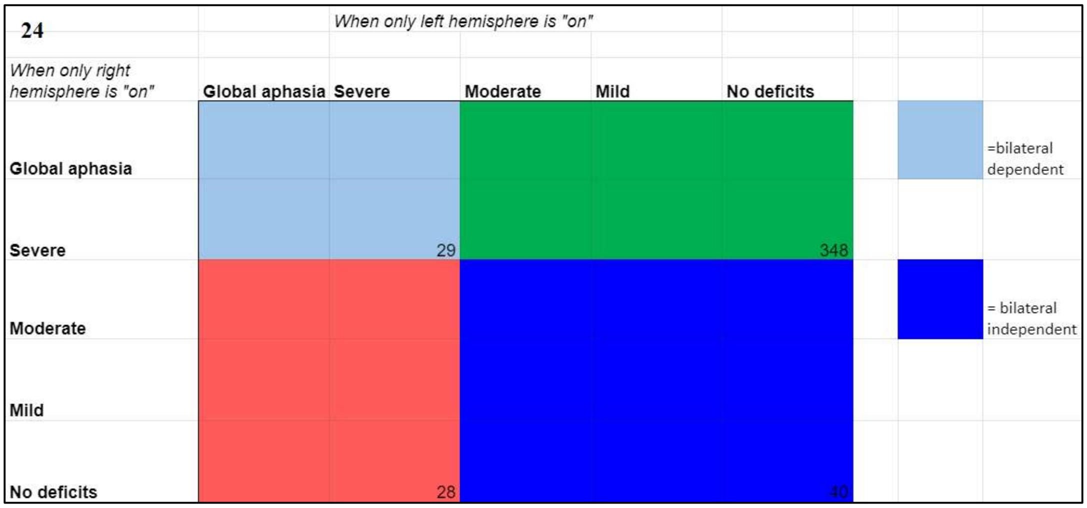
    Qualifying condition: Epilepsy patients undergoing Wada tests for presurgical evaluation.

Radiological evidence of brain lesion: Yes. Out of the 445 patients, 349 had lesions detected via MRI. The nature of the lesions is detailed in Tables 4–6, on p. 1510–1511.

Lateralization categories source: p. 1506–1507, in the "Language lateralization" section. In this study, laterality categories were determined entirely by speech arrest times. However, the researchers created three different measures of speech arrest in order to make laterality decisions. A patient was classified as having left-hemisphere or right-hemisphere dominance if they met two of the three measures, and all other patients "were assumed to have bilateral language representation." Those bilateral patients were then "subdivided into bilateral-dependent (BD), if absolute speech arrests times were ≥ 60 s after both left and right injections, and bilateral-independent (BI), if speech arrest time was < 60 s after either the left or right injection." These are the three lateralization measures: "(1) the absolute duration of the speech arrest after left and right intracarotid barbiturate injection, with the criteria being greater than 60 s on one side and less than 60 s on the other; (2) the difference between speech arrest times after left and right injections (tL - tR), using a cutoff of 30 s; and (3) the laterality index, defined as the difference between speech arrest times after left and right injections, divided by the sum of speech arrest times after left and right injection [(tL - tR)/(tL + tR)], using a cutoff of 0.5."

Distribution source: p. 1507, in the last sentence of the top paragraph on the right-hand side. Left-hemisphere dominant: 348; right-hemisphere dominant: 28; bilateral dominant: 29; bilateral independent: 40.

Matrix composition rationale: We used MATLAB to code those three conditions. We mirrored the basic construction of the MATLAB plot on the matrix, but decided that speech arrest from 20 seconds to one minute would potentially constitute a moderate deficit (i.e., we decided that it could represent anywhere from no deficit to a moderate deficit). Supposedly, a patient can have a 20 second period of speech arrest and that's completely normal. We also distinguished between bilateral dependent and bilateral independent.



25. **Article:** Memory performance is related to language dominance as determined by the intracarotid amobarbital procedure

    Authors: Kovac, S., Möddel, G., Reinholz, J., Alexopoulos, A. V., Syed, T., Schuele, S. U., Lineweaver, T., & Loddenkemper, T.

    Handedness: Not reported.

    Qualifying condition: p. 146, in Table 1. All of the patients had epilepsy. The nature of the epilepsy varied; 140 had left-sided, 118 had right-sided, 17 had bilateral, and 5 had unspecified.

    Radiological evidence of brain lesion: Yes. The researchers state “Lesions were identified by MRI in 296 (76.7%) patients. Lesions were found to be left in 155 (52.4%), right in 114 (38.5%), and bilateral in 27 (9.1%) patients” (p. 146, in the “Imaging Findings” section). The nature of the lesions is detailed in Table 2.

    Lateralization categories source: p. 146, in the "2.5. Language lateralization" section. The researchers state that "language lateralization was quantified based on speech arrest." They used a laterality index, defined as "the difference between speech arrest times after left (tL) and right (tR) injections, divided by the sum of speech arrest times after left and right injections [(tL - tR) / (tL + tR)]. Positive values indicate left-sided lateralization, whereas negative values indicate right-sided lateralization." They provide three lateralization measures, and right/left language dominance is only classified if a patient's IAP met two out of three of the measures. If a patient did not meet two out of the three measures, they were classified as "bilateral language dominant with absolute speech arrest times of ≥ 60 seconds after both left and right injections, and bilateral independent with speech arrest time < 60 seconds after either left or right injection." The three measures are as follows: "(1) the absolute duration of the speech arrest after left and right intracarotid barbiturate injection being greater than 60 seconds on one side and less than 60 seconds on the other' (2) the difference between left and right injection speech arrest times (tL - tR) with a cutoff of 30 seconds; and (3) the LI."

Distribution source: p. 146, in the "3.1.3. Language lateralization" section. Left-hemisphere dominant: 307; right-hemisphere dominant: 23; bilateral dependent: 26; bilateral independent: 30.

Matrix composition rationale: We decided to use the same matrix configuration as that of Moddel et al. (2009). For Moddel et al. (2009), we used MATLAB to code those three conditions. We mirrored the basic construction of the MATLAB plot on the matrix, but decided that speech arrest from 20 seconds to one minute would potentially constitute a moderate deficit (i.e., we decided that it could represent anywhere from no deficit to a moderate deficit). Supposedly, it's normal for a patient to have a 20 second period of speech arrest even if their language abilities are present in the tested hemisphere. We distinguished between bilateral dependent and bilateral independent.

26. **Article**: Hemispheric lateralization and language skill coherence in temporal lobe epilepsy

    Authors: Tracy, J. I., Waldron, B., Glosser, D., Sharan, A., Mintzer, S., Zangaladze, A., Skidmore, C., Siddiqui, I., Caris, E., & Sperling, M. R.

    Handedness:

    Right-handed: 92

    Left-handed or ambidextrous: 32

    Calculated from Table 1 on p. 1180.

    Qualifying condition: Medial temporal lobe epilepsy

    Radiological evidence of brain lesion: Not fully addressed. The researchers state: “While we did take into account key variables including age of seizures onset, age at first risk for seizures, and lesion lateralization (side of ictal focus), we did not study other factors that can influence speech reorganization such as the role of specific brain pathology and its location…” (p. 1186–1187). See Table 2 on p. 1180 for temporal lobe neuropathy details.

    Lateralization categories source: p. 1181, in the lowermost paragraph on the right side and the second paragraph on the left side. The researchers state: "analyses for a given task always excluded cases with forms of negative bilaterality defined as incompetence with both injections (both scores of zero) or as incompetence with one injection (score of zero) and only partial competence with the other (score of one). For each skill, we also classified hemispheric representation into three groups (note, hemisphere scores are based on amytal injections to the opposite hemisphere): typical dominance (left hemisphere score of two, right hemisphere score of zero), right hemisphere dominance (a right hemisphere score of two, and a left hemisphere score of zero or one), and bilateral (scores of two or one for both hemispheres, or a left hemisphere score of two and a right hemisphere score of one)." The authors also explain: "For several analyses, to increase statistical power we combined the right hemisphere and bilateral groups, and when doing so refer to them as the atypical dominance group. Regarding how scores (e.g., 0, 1, or 2) were assigned, the authors state: "a score of two was given for correct, error free performance (proficient performance). For each skill a score of one was given for performance demonstrating competence with infrequent errors (no more than one) during comprehension responses, repetition responses, reading (no more than one misreading or 'non-response' out of the total three words), and naming (no more than one misnamed or 'non-response' out of the three objects presented). One point responses were considered to reflect partial competence. A score of zero was given for error prone responses exceeding the limits of a one point score (e.g., two errors or no response on two or more items within a skill). This zero score is referred to as incomplete performance."

Note: This article discusses *both* a laterality index method of determining laterality from a patient's performance on each language task as well as the method described above. However, after reviewing this article several times, we determined that the reported laterality distribution (i.e., distribution on p. 1182) was produced from the method described above. Thus, although Tracy et al. report the same LI as several other articles we've reviewed, we did not use the same matrix configuration for this article as we used for those. Also, this article only reports distributions for each of their five assessed areas of language (i.e., reading, naming, comprehension, repetition, and speech). For those five distributions, it only reports patients as typical (i.e., left-hemisphere dominant) or atypical (i.e., bilateral or right-hemisphere dominant).

Distribution source: p. 1184, in Figure 3. To obtain the distributions for each language skill, we used the percentages listed in the "Grand Mean" bar for each graph. We multiplied those percentages by the *n* listed under "Grand Mean" (e.g., 115 for the comprehension graph and 116 for the speech graph). We found the number of patients categorized as "excluded cases" by subtracting each *n* from 124, which was the total *n* for the study.

<u>Comprehension</u>: Left: 90.85; Right: 9.2; Bilateral: 14.95; Excluded: 9

<u>Repetition</u>: Left: 94.3; Right: 6.9; Bilateral: 13.8; Excluded: 9

<u>Speech</u>: Left: 97.44; Right: 9.28; Bilateral: 9.28; Excluded: 8

<u>Reading</u>: Left: 65.66; Right: 7.84; Bilateral: 24.5; Excluded: 26

<u>Naming</u>: Left: 67.45; Right: 7.6; Bilateral: 19.95; Excluded: 29

Matrix composition rationale: A score of 2 represents "full skill," and the researchers state that a score of 2 for both hemispheres denotes bilaterality. Thus, the cell in which the "No Deficits" column and row intersects must be bilateral. The researchers also state that a score of 1 for both hemispheres denotes bilaterality. A score of 1 represents "incomplete skill" and was defined as no more than one error for a set of tasks (e.g., a set of comprehension tasks, reading tasks, naming tasks, etc.). We decided that a score of 1 should correspond with both "Mild Deficits" and "Moderate Deficits" on the matrix. (For example, if a patient was asked to read three words and did not respond at all to one of the three, these researchers would assign that patient a 1 for the reading task, and we would consider that behavior to be indicative of a moderate impairment. If the patient had perhaps been given 25 words to read and only failed to respond to one, we might consider the patient to have only mild impairment. But, with a field of only three words, we feel that such a response can be indicative of a mild *or* moderate impairment. Moreover, if the patient had merely made a phonemic error on one of the three words, they would be assigned a 1, and we would consider that indicative of mild impairment.) Thus, the four cells where the "Mild Deficits" and "Moderate Deficits" columns and rows intersect must be bilateral. Also, as the authors state that bilaterality is also denoted by "a left hemisphere score of two and a right hemisphere score of one," the cells in which the "No Deficits" column and "Mild Deficits" and "Moderate Deficits" rows intersect must be bilateral. The researchers also specify the following: "analyses for a given task always excluded cases with forms of negative bilaterality defined as incompetence with both injections (both scores of zero) or as incompetence with one injection (score of zero) and only partial competence with the other (score of one)." Since the researchers include "non-response" as part of their definition of a 0 score, and "Global Aphasia" is the correlate to this on our matrix, the cell where the "Global Aphasia" row and columns meet is an 'excluded case.' We have indicated this with the color gray. In the same way, as a 0 score was given for "error prone responses exceeding the limits of a one point score," which they explain can even be "two errors within a skill," we feel that a score of 0 also corresponds with "Severe Deficits" on our matrix. Thus, the cells in which the "Severe Deficits" and "Global Aphasia" rows and columns meet are also gray. Finally, to account for the fact that a score of 0 on one injection and a score of 1 on the other injection for a single skill is considered an excluded case, and we've established that a score of 1 corresponds with both "Moderate Deficits" and "Mild Deficits" on our matrix, we've made the cells for which the row is "Global Aphasia" or "Severe Deficits" and the column is "Moderate Deficits" or "Mild Deficits" (as well as the complement) gray. Right-hemisphere dominance is defined as "a right hemisphere score of two, and a left hemisphere score of zero or one." We've established that a 2 corresponds with "No Deficits" while the set of 0 and 1 together correspond with "Global Aphasia," "Severe Deficits," "Moderate Deficits," and "Mild Deficits." So, on the matrix, right-hemisphere dominance is comprised of the "No Deficits" row and all of the columns except the "No Deficits" column. Left-hemisphere dominance is then defined as "left hemisphere score of two, right hemisphere score of zero," rather than the complement of the right-hemisphere definition. Thus, left-hemisphere dominance is represented by the cells in which the "No Deficits" column and the "Severe Deficits" and "Global Aphasia" rows intersect.

27. **Article**: The intracarotid amobarbital or Wada test: unilateral or bilateral?

    Authors: Uijl, S. G., Leijten, F. S. S., Arends, J. B. A. M., Parra, J., van Huffelen, A. C., van Rijen, P. C., & Moons, K. G. M.

    Handedness: Not reported.

    Qualifying condition: All patients had temporal lobe epilepsy.

    Radiological evidence of brain lesion: p. 202 in Table 1. Yes. In 47 patients, MRI revealed mesial temporal sclerosis, and in 27 patients, MRI revealed another lesion.

    Lateralization categories source: p. 200, in the second paragraph of the "Intracarotid amobarbital procedure" section, the researchers define "language dysfunction" in terms of behavior during their language assessment items. They define it as "the occurrence of dysnomia, paraphasia or incongruous mistakes on comprehension tasks after injection." However, they never explain exactly how that definition then translates into their laterality categories (i.e., left, right, and bilateral).

    Distribution source: p. 201, in the "Language lateralization" section of Table 1. Left-hemisphere dominance: 87; Right: 6; Bilateral: 7.

    Matrix composition rationale: Matrix could not be built.

Note: Could not build a matrix for this article, but its distribution information was included in quantitative analysis.

28. **Article**: Language dominance and mapping based on neuromagnetic oscillatory changes: comparison with invasive procedures

    Authors: Hirata, M., Goto, T., Barnes, G., Umekawa, Y., Yanagisawa, T., Kato, A., Oshino, S., Kishima, H., Hashimoto, N., Saitoh, Y., Tani, N., Yorifuji, S., & Yoshimine, T.

    Note: Could not build a matrix for this article and distribution information was not included in quantitative analysis.

29. **Article:** Visual naming performance after ATL resection: Impact of atypical language dominance

    Authors: Kovac, S., Möddel, G., Reinholz, J., Alexopoulos, A. V., Syed, T., Koubeissi, M. Z., Schuele, S. U., Lineweaver, T., Busch, R. M., & Loddenkemper, T.

    Handedness:

    Right-handed: 89

    Left-handed: 10

    Note: Handedness information was only available for 99 of the total 101 patients. It was obtained from Table 1, on p. 2222.

    Qualifying condition: All patients had temporal lobe epilepsy. There were 50 with left temporal lobe epilepsy and 51 with right temporal lobe epilepsy.

    Radiological evidence of brain lesion: p. 2222, in Table 1. There were 86 patients with evidence of brain lesion via MRI. More specific information about the lesions is not provided.

    Lateralization categories source: P. 2222, in the "2.5. Language Lateralization" section. Language lateralization was based on speech arrest times. The researchers used three lateralization measures: "(1) The absolute duration of the speech arrest after left and right intracarotid barbiturate injection being greater than 60s on one side and less than 60s on the other;

(2) the difference between right and left injection speech arrest times (tL - tR) with a cut-off of 30s; and (3) the laterality index (LI). The LI equation was as follows: [(tL - tR) / (tL + tR)], with a cut-off of 0.5. The researchers explain: "Left or right language dominance was classified in the remaining patients with bilateral dependent (BD) language dominance showing absolute speech arrests times of ≥ 60s and bilateral-independent (BI) of < 60s after either injection."

Note: Although Kovac et al. give this description of lateralization categories, which includes definitions for right language dominance and the two categories of bilateral dominance, they only report a distribution for left-hemisphere dominance and atypical dominance. That is the focus of this paper. Kovac et al. (the exact same research team) also published a paper in 2009, which is included in this study, and that paper reported a distribution for all four categories (i.e., left, right, bilateral dependent, and bilateral independent). In this paper, they clarify, in the second sentence of the "2.5 Language lateralization" section on p. 2222, that their atypical category is the combination of the right and bilateral categories.

Distribution source: P. 2222, in the topmost paragraph on the left-hand side. We added the number of left-hemisphere dominant left TLE patients to the number of left-hemisphere dominant right TLE patients, and the number of atypical dominant left TLE patients to the number of atypical dominant right TEL patients. Left-hemisphere dominant: 84; atypical dominant: 17. (n = 101).

Matrix composition rationale: We decided to use the same matrix configuration as that of Moddel et al. (2009), combining that matrix's right-hemisphere dominance, bilateral dependent, and bilateral independent areas into a single atypical area here. For Moddel et al. (2009), we used MATLAB to code the three conditions. We mirrored the basic construction of the MATLAB plot on the matrix, but decided that speech arrest from 20 seconds to one minute would potentially constitute a moderate deficit (i.e., we decided that it could represent anywhere from no deficit to a moderate deficit). Supposedly, it's normal for a patient to have a 20 second period of speech arrest, even when their language abilities are present in the tested hemisphere. We also distinguished between bilateral dependent and bilateral independent.

29	When only left hemisphere is "on"				
When only right hemisphere is "on"	Global aphasia	Severe	Moderate	Mild	No deficits
Global aphasia					84
Severe					
Moderate					
Mild		17			
No deficits					

30. **Article**: Evidence for the solidarity of the expressive and receptive language systems: A retrospective study

Authors: Moser, D. C., Papanicolaou, A. C., Swank, P., & Breier, J. I.

Handedness:

Right-handed: 264

Left-handed: 30

Ambidextrous individuals: 2

Qualifying condition: Epilepsy patients with intractable seizures, who were candidates for surgical resection. There were 137 patients with left temporal pathology, 23 patients with left frontal pathology, 119 patients with right temporal pathology, and 17 patients with right frontal pathology.

Radiological evidence of brain lesion: Yes. Patients had lesions as described above, but the researchers do not provide additional details.

Lateralization categories source: p. 64, in first and second paragraph of the "Data Analysis" section. The researchers state: "Patients were categorized as having typical language lateralization (i.e., LH dominance) for each language system (expressive and receptive) when performance of the LH was good and performance of the RH was poor. Patients were categorized as having atypical lateralization (i.e., not LH dominance) when they presented any other pattern of performance (i.e., good performance with either hemispheres = bilateral competence; poor performance with each hemisphere = partial reliance; and poor performance with LH/good performance with RH = *RH dominance*)." The researchers define their terms in the following passage: "The language competence of each hemisphere was deemed *good* if performance was without error (i.e., score of 0) or mildly deficient (i.e., score of 1) and *poor* if performance was moderately or severely impaired (e.g., score of 2 or 3; paraphasias, speech arrest, or inability to produce accurate response to commands)."

Distribution source: p. 64, in Table 1. The researchers report separate distributions for expressive and receptive language abilities, and they divide these distributions into the patients who had left hemisphere pathology and the patients who had right hemisphere pathology. We obtained the distribution numbers by applying each *n* (i.e., the *n* for patients with left hemisphere pathology and the *n* for patients with right hemisphere pathology) to its respective "Total" percentages column to determine its expressive language distribution, and its respective "Total" percentages row to determine its receptive language distribution. The breakdown was as follows:

<u>Left hemisphere pathology; expressive</u>: Left hemisphere dominance: 108.8; Bilateral competence: 22.4; Partial reliance: 6.4; Right hemisphere dominance: 22.4

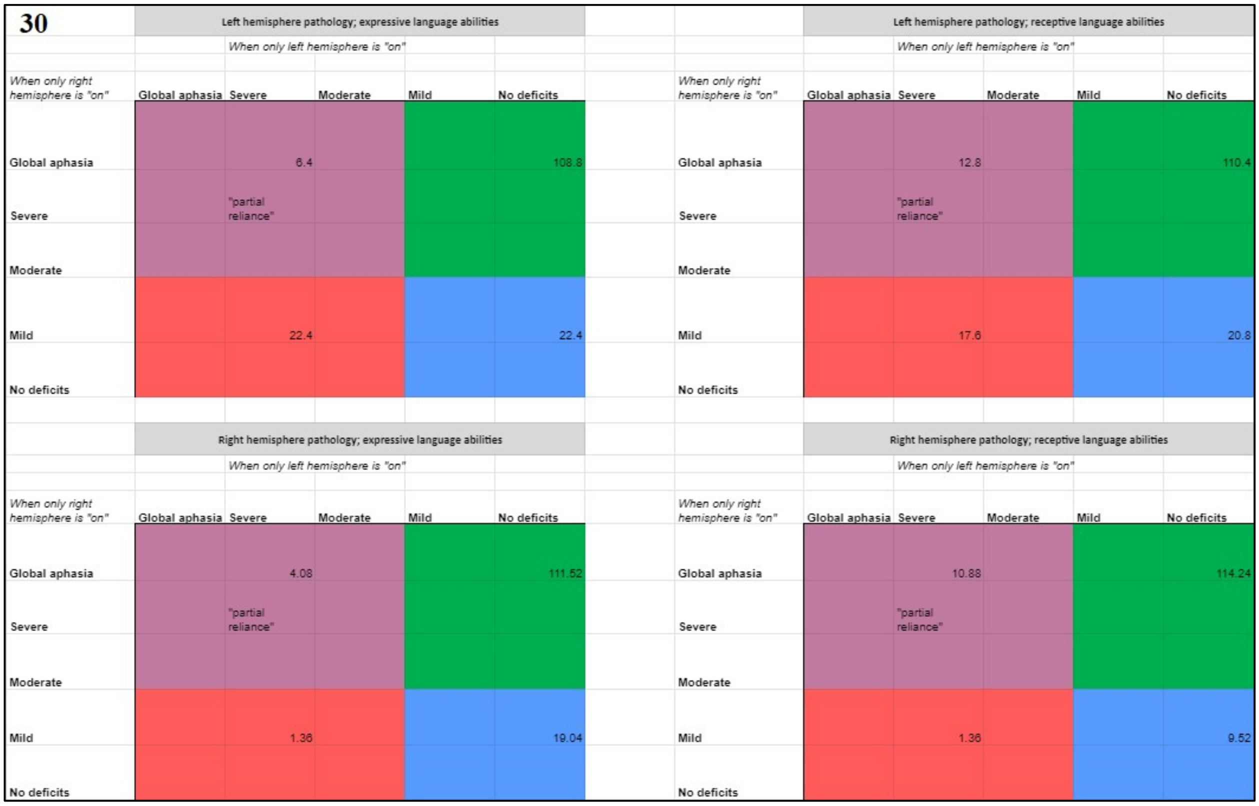
<u>Left hemisphere pathology; receptive</u>: Left hemisphere dominance: 110.4; Bilateral competence: 20.8; Partial reliance: 12.8; Right hemisphere dominance: 17.6

Note: There is a conflict in the presented data here. These numbers should add to 160, but they add to 161.6.

<u>Right hemisphere pathology; expressive</u>: Left hemisphere dominance: 111.52; Bilateral competence: 19.04; Partial reliance: 4.08; Right hemisphere dominance: 1.36

<u>Right hemisphere pathology; receptive</u>: Left hemisphere dominance: 114.24; Bilateral competence: 9.52; Partial reliance: 10.88; Right hemisphere dominance: 1.36

Matrix composition rationale: For a patient to be considered as having left-hemisphere dominance, he or she must have demonstrated no language deficits or mild language deficits when the left hemisphere was active and, as per the researcher's description, moderate to severe deficits when the left hemisphere was anesthetized. We do not think the argument can be made that our matrix's "Mild" category falls within the realm of the researchers' description of moderate to severe impairment (i.e., "paraphasias, speech arrest, or inability to produce accurate response to commands") because they themselves had a score for "mild" deficits, which they presumably assigned at times. The researchers define right hemisphere dominance as "poor" performance when only the left hemisphere is active and "good" performance when only the right hemisphere is active. As the researchers' term "good" denotes no error or mild deficits (e.g., a score of 0 or 1) and the term "poor" denotes moderate or severe impairment (e.g., score of 2 or 3), the right hemisphere dominance section consists of the cells for which "No Deficits" and "Mild Deficits" on the right hemisphere and "Global Aphasia," "Severe Deficits," and "Moderate Deficits" on the left hemisphere converge. (Note: The researchers do not discuss global aphasia, but their "severe" term is their most extreme; it denotes a score of 3, which is the highest score given. This is why we chose to include the "Global Aphasia" column even though the researchers only used the term "severe"). The category of partial reliance is defined as poor performance with each independent hemisphere, so it occupies the cells where the "Global Aphasia," "Severe Deficits," and "Moderate Deficits" rows and columns converge. The category of bilateral competence is defined as "good performance with either hemispheres." The grammar of that definition is unclear, however, we think the best interpretation of that definition, given the researcher's definitions for the other laterality categories, is good performance (i.e., no deficits or mild deficits) with both hemispheres. Thus, the bilateral area is where the "No Deficits" and "Mild Deficits" columns and rows intersect.



31. **Article**: Cortical stimulation mapping and Wada results demonstrate a normal variant of right hemisphere language organization

Authors: Drane, D. L., Roraback-Carson, J., Hebb, A. O., Hersonskey, T., Lucas, T., Ojemann, G. A., Lettich, E., Silbergeld, D. L., Miller, J. W., & Ojemann, J. G.

Handedness:

Right-handed: 30

Left-handed or ambidextrous: 59

Calculated from "Subjects" section on p. 4.

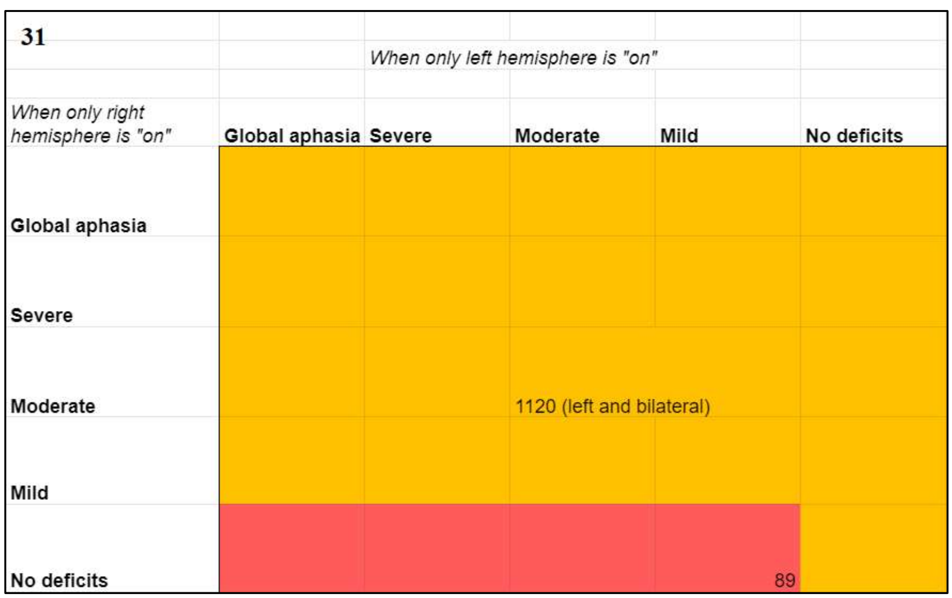
Qualifying condition: All patients were epilepsy patients undergoing preoperative assessment.

Radiological evidence of brain lesion: Not reported. The researchers state: “One limitation of the current study is that neuroimaging techniques have changed drastically over the period examined. Therefore, we could have missed subtle left-hemisphere pathology in some of the patients (particularly the earliest patients). However, our suggestion that the occurrence of RH language in this patient cohort is a normal variant rather than a pathological shift in function rests as much on behavioral patterns and evidence of structural/functional pathology in the RH. Of note, we had 3T MRI data on three of our right-handed patients with RH speech (half of our cryptogenic cases), and no structural abnormalities were observed on any of these scans” (p. 8, in the “Discussion” section).

Lateralization categories source: pp. 5–6, beginning 9 lines from the bottom of the page, in the "Wada Procedure" section. The researchers state: "Patients were classified as having unilateral speech if language performance during a single injection differed from their baseline nondrug performance. All of the patients in the current sample experienced naming errors, but also often exhibited speech arrest and an inability to follow the simple instructions built into the repetitive tasks (auditory comprehension), reading errors, and positive signs of aphasia (e.g., paraphasic errors). [...] A patient would be said to have bilateral language if disruption occurred in any language behavior on both the left and right injections or if performance remained normal following both injections. Of note, the latter pattern of performance was never observed in the sample described, but instead reflects our theoretical position. [...] Exclusive right hemisphere language was determined by the presence of language dysfunction which occurred with the right injection but was absent with the injection on the left (i.e., the left injection did not produce any significant changes from nondrug baseline)."

Distribution source: p. 4, in the "Subjects" section. There were 1209 interpretable Wada tests and 89 of those "were shown to have exclusive RH dominant language." Thus, we concluded that 1,120 patients either had left-hemisphere dominance or were bilateral, and 89 had right-hemisphere dominance.

Matrix composition rationale: If a patient demonstrated any language deficit (ranging from mild to global aphasia) on both IAPs, they would be designated as having bilateral dominance. Thus, all of the cells in which any deficit in one hemisphere intersects with a deficit in the other is designated as bilateral. Additionally, as per the researchers' description, the demonstration of no deficits when both hemispheres were anesthetized would result in a designation of bilateral. Right- and left-hemisphere dominance is then restricted to the remaining cells. As these researchers defined unilateral dominance as the patient performing at their baseline when the non-dominant hemisphere was anesthetized but "language dysfunction" when the dominant hemisphere was anesthetized, we made the "No Deficits" column represent a patient's baseline. Moreover, since the researchers did not specify how severe errors needed to be to qualify as "language dysfunction," we assumed that those errors could have ranged from mild to global aphasia.



32. **Article:** Language lateralization by fMRI and Wada testing in 229 epilepsy patients: Rates and predictors of discordance

Authors: Janecek, J. K., Swanson, S. J., Sabsevitz, D. S., Hammeke, T. A., Raghavan, M., Rozman, M. E., & Binder, J. R.

Handedness:

Right-handed: 185

Left-handed or ambidextrous: 44

Calculated from Table 4, on p. 18.

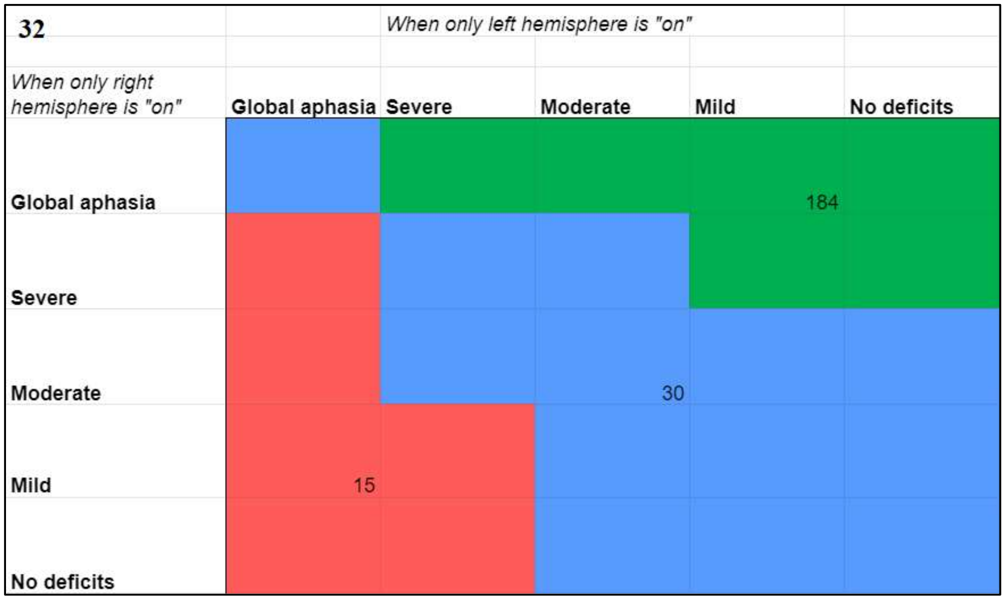
Qualifying condition: All patients had epilepsy, valid and complete fMRI data, and had not had previous temporal resection.

Radiological evidence of brain lesion: Yes. There were 105 patients who had mesial temporal sclerosis or hippocampal atrophy. This was calculated from Table 1, on p. 18.

Lateralization categories source: p. 3–4, in the "Wada Testing" and "Operational Definition of Discordance" sections. The authors account for their use of an LI here: "The scores for each language task ranged from 0–3, with lower scores indicating a greater degree of impairment. The total possible, or maximal obtainable, score therefore varied depending on the duration of hemianesthesia. LIs were calculated as the difference between the percent of maximal obtainable score in the inject right/test left condition and the percent of maximal obtainable score in the inject left/test right condition. LIs ranged from +100 (indicating complete left hemisphere dominance) to -100 (indicating complete right hemisphere dominance). These quantitative LIs were used to define language dominance in subsequent clinical decision-making." The authors explain their ranges here: "As Wada language lateralization estimates are not available for neurologically normal individuals, we set the Wada cut score to yield similar proportions of left, bilateral, and right dominant cases as fMRI. Of note, the kurtosis of the LI distributions for Wada and fMRI are different. Accordingly, Wada language dominance was categorized using a cut score of 50: left (LI ≥ 50), right (LI ≤ -50), and bilateral (LI between -50 and 50)."

Distribution source: Table 1, in the bolded row that shows the Wada distribution numbers. Left = 184; Bilateral = 30; Right = 15.

Matrix composition rationale: We used MATLAB to plot this matrix.



33. **Article**: A voxel-based asymmetry study of the relationship between hemispheric asymmetry and language dominance in Wada tested patients

Authors: Keller, S. S., Roberts, N., Baker, G., Sluming, V., Cezayirli, E., Mayes, A., Eldridge, P., Marson, A. G., & Wieshmann, U. C.

Handedness: Not reported. (Handedness was reported in terms of the Edinburgh Handedness Inventory (EHI), and the means for different patient groups are in Table 1 on p. 3036, but the researchers did not provide a handedness distribution).

Qualifying condition: All patients had medically intractable focal epilepsy. The researchers state: “Of the 135 patients, 123 (91%) had presumed TLE (69 left, 46 right, two bilateral, six undetermined laterality) and 12 (9%) had an extratemporal focus (six left, three right, three undetermined laterality)” (p. 3034).

Radiological evidence of brain lesion: Not reported.

Lateralization categories source: p. 3034, at the bottom of the second paragraph in the "Wada procedure" section. The authors state: "The side of HLD was determined by the patient's ability to understand and produce language on the above measures during hemianesthesia; language was considered to be unilateral following injection into a hemisphere where there was interrupted speech output and impaired comprehension with a significant failure to recall information for the tasks presented compared to injection into the contralateral hemisphere where speech production and comprehension were intact. Language was considered bilateral when there were no obvious differences in the performance following injection to either hemisphere."

Distribution source: P. 3036, in the "3.1 Wada test and clinical data" section. The authors state: "One hundred and fourteen (84.4%) patients has left HLD, 10 (7.4%) right HLD, and 11 (8.2%) bilateral language representation."

Matrix composition rationale: As the researchers define language bilaterality as "no obvious differences in the performance" for right and left injection, without specifying the possible severity or mildness of that performance, every cell for which the right hemisphere and left hemisphere display the same performance will be designated as bilateral. Regarding unilateral dominance, the researchers' included performance on a recall task as part of their definition for right- and left-hemisphere dominance. We find this problematic. Recall tasks rely, at least in part, on memory ability rather than language ability. So, we've composed the right- and left-hemisphere dominance spaces based on the other part of the researchers' definition—that of interrupted speech output and impaired comprehension with one injection and intact speech production and comprehension with the other. Since the researchers do not specify the possible severity or mildness of the speech interruption and impaired comprehension, we have made the assumption that they could range from mild to global aphasia. Moreover, we have assumed that when the researchers use the term "intact," they mean without any deficits.

33	When only left hemisphere is "on"				
When only right hemisphere is "on"	**Global aphasia**	**Severe**	**Moderate**	**Mild**	**No deficits**
Global aphasia					114
Severe					
Moderate			11		
Mild					
No deficits	10				