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The electrophysiology of aphasia: A scoping review

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HIGHLIGHTS

- Consistent patterns of reduced amplitude, delayed latency, and different distribution in people with aphasia compared to controls.
- Event-related potentials (ERPs) shown to be modulated by severity of aphasia.
- Need for improved consistency and cohesiveness in ERP methodology as a basis for a more reliable and valid clinical tool.

ABSTRACT

Objective: To systematically assess the body of literature using N400 and P600 as they relate to people with aphasia. The primary aim was to reveal patterns in the literature which could be used to direct future research in the development of clinically relevant Event-Related Potentials (ERPs) for language assessment, while also identifying gaps in existing knowledge and highlight areas of further inquiry.
Methods: A literature search was performed on studies published before May 2021. Relevant studies on aphasia and the two ERPs of interest were assessed for quality, and the relationship between aphasia and these ERPs was explored.
Results: A total of 721 articles were identified, with 30 meeting inclusion criteria. Although there is significant variation in the literature, this scoping review revealed people with aphasia show reduced amplitude, delayed latency and different distribution compared to controls, and that ERPs are modulated by severity of aphasia.
Conclusions: To develop a relevant clinical tool for the management of aphasia, future research must strive to improve consistency within ERP methodology, with a greater number of diverse aphasia subtypes included in research.
Significance: This scoping review reveals N400 and P600 represent promising potential biomarkers for the diagnosis and ongoing management of aphasia.

1. Introduction

Aphasia is the term used to describe an acquired language difficulty, as a result of injury to the language centres in the brain (Benson and Ardila, 1996). Most commonly, aphasia is concomitant with a left cerebral hemisphere stroke and occurs in approximately 30–45% of all stroke cases (Pedersen et al., 1995; Kauhanen et al., 2000; Pedersen et al., 2004; Engelter et al., 2006; Dickey et al., 2010). As aphasia is a language disorder, the severity and degree of disruption to language processing modalities is widely heterogenous. Typically, aphasia affects language expression and comprehension in all the primary modes of linguistic communication. As a result, an individual may experience difficulty with their ability to produce and understand spoken language, as well as their ability to produce and understand written and signed languages.

Best practice stipulates that those admitted to hospital following a brain injury who are exhibiting signs of communication deficits, should have their speech and language abilities assessed by a speech language therapist (SLT) (SFNZ, 2010). Early and continued assessment of an individual's speech and language post-stroke provides information about the severity of the impairment, offers prognostic insight to the rate of recovery, and guides rehabilitative planning (AARP, 2014). However, currently there is inconsistency within and across clinical practice in the assessment of communication skills. An individual's language functioning post-stroke is assessed through a variety of clinical measures and assessments,

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most commonly via administration of a bedside language assessment. El Hachioui, et al (2017) conducted a systematic review which examined the diagnostic validation of commonly used language screening tests in post-stroke settings. The authors found, despite a number of screening tests being available, many of the tests lacked any proper verification of diagnostic validity. Similarly, Rohde et al. (2018) reviewed the diagnostic capabilities of 56 language tests commonly used by SLTs as a tool to diagnose post-stroke aphasia. The review determined that none of the included language tests were diagnostically validated for their intended diagnostic purposes. Foster et al. (2016) interviewed SLTs in an exploration of the aphasia management pathway. All participants revealed that assessment was a driving component of speech language therapy when working with this population. However, the study found methods for assessing people with aphasia greatly varied across locations and clinicians. The most commonly reported means of assessment was an informal screening of a patient's communication functioning, which was typically a tool developed by individual clinicians that lacked any diagnostic validity or standardisation. This study echoes earlier work by Vogel et al. (2010) who investigated clinician practices in aphasia throughout Australia and New Zealand. In their survey of 174 SLTs, the authors determined the majority of practising clinicians used subjective and/or un-standardised assessments to assess the communication skills of individuals with aphasia. Considering the importance of an accurate diagnosis of aphasia in patient care, this literature suggests that more work is required to aid clinicians in their assessment and diagnostic decision-making of patients with aphasia.

In recent years, there has been an uptake in the investigation of biomarkers for neurological conditions. A biomarker is a measure of a structural or functional difference which can be objectively quantified and reproduced to be used in diagnosing and monitoring a disease or disorder (Strimbu and Tavel, 2010). In the realm of speech, language, and hearing sciences electroencephalography (EEG) and event-related potentials (ERPs) offer great diagnostic potential due to their affordability, convenience, and temporal resolution.

EEG is a neurophysiological methodology where electrodes are placed onto the scalp to continuously record the electrical activity of the brain. ERPs represent the summation of synchronous electrical activity of neural processing in response to a time-locked stimulus, averaged over a number of trials of the same type. Various stimuli are used in EEG experimental paradigms to elicit and investigate the neural basis of specific sensory, cognitive, or motor events, which appear as a cycle of interchanging positive and negative voltage waves, referred to as ERP components. Typically, ERPs are characterised by their amplitude, latency, and topography. Amplitude refers to the proportion of neuronal activity related to a given event, whereas latency reflects the timing of the underlying processes. Topography reveals the distribution of electrical activity over the scalp (Luck, 2014; Kotz and Friederici, 2003). These neurophysiological measures offer insight into the speed of processing and can highlight connectivity issues. The focus of the present scoping review is two cognitive ERP components which occur in the later stages of processing: namely N400 and P600.

The N400 and P600 have become two of the most prominent ERP components to be studied in the field of language comprehension. The N400 is a centro-parietally distributed negative wave which peaks around 400 ms after the onset of a stimulus. Kutas and Hillyard (1984) first described the component in their landmark study involving semantically anomalous words. It is now widely accepted that the N400 component can be elicited by any stimuli from which meaning can be ascertained. N400 activity has been seen in response to words in numerous languages and all modalities, as well as pictures, environmental sounds, and faces. The amplitude of this component has an inverse relationship with the degree of expectancy of a stimulus generated by the preceding context. That is to say, the less a word is expected given the context of a sentence, the larger the N400 will be. Its relationship to meaning has resulted in N400 traditionally being viewed as an index of semantic integration (Hagoort, 2003, 2008), with a higher amplitude reflecting a greater difficulty of integrating semantic information. More recently, N400 has been theorised as an index of lexical access and retrieval from semantic memory (Brouwer et al., 2012; Kutas and Federmeier, 2000). While N400 and P600 are two of the most prevalent ERPs used in language research, they are by no means the only components to be studied in relation to language, particularly in a clinical context. Recent research has shown the components Mismatch Negativity (MMN) and P300 have promise because of their sensitivity to subtle language deficits in post-stroke aphasia (De Letter et al., 2021; Cocquyt et al., 2020; Lucchese et al., 2017; Mohr et al., 2016). Similarly, LAN (left anterior negativity) has been shown to be sensitive to violations of language, particularly grammatical violations. However, there is still debate about whether this component reflects processes which are specific to syntax or are indicative of working memory (Hagoort et al., 2003a,b; Kluender and Kutas 1993a, b; Coulson et al. 1998). Commonly, LAN is followed by the P600.

The P600 is positive travelling wave with a centro-parietal distribution which peaks around 600 ms post stimulus onset. A long-standing view has held the P600 as an index of syntactic revision and repair, because an increased amplitude in the P600 response has been observed in relation to syntactic violations or ambiguities (Osterhout and Holcomb, 1992; Osterhout et al., 1994; Friederici et al., 2002). However, similar to the N400, views on the P600 are shifting. More recent studies have shown the P600 response to be present in the absence of syntactic violations, with the component instead being elicited by implausible but grammatical stimuli which are commonly associated with the N400 response. More recently, the P600 has been posited to index the integrative aspect of language processing (Brouwer et al., 2012)

Despite the ongoing debate around these two ERP components, there is unanimous agreement that both the N400 and P600 have a strong relationship to language processing. They are therefore prime candidates for potential biomarkers in the diagnosis and monitoring of aphasia. Language happens at an exceptionally rapid rate, so EEG methodology is ideal to capture electrical activity in the brain at the millisecond-level, compared to other brain imaging techniques. Furthermore, unlike techniques which are not viable for patients with electronic or artificial medical implants (e.g. a pacemaker), anxiety related to confined spaces, tattoos, higher body mass index, and/or other complications, EEG is not prohibited. EEG also offers the possibility to assess populations where behavioural paradigms are ill-suited or difficult to administer. Building upon this, EEG has the potential to not only reflect the neural underpinnings of behaviour, it may aid in elucidating the underlying cause of language impairment.

While EEG has numerous advantages, which could be applied to clinical settings, it requires a high level of reliability. Currently, this research is still in its infancy, and more work is needed to make these potential biomarkers a clinically meaningful and valid method of assessing language functioning. That being said, the clinical use of EEG and ERPs is promising, as technologies continue to become more affordable, quick to set up, and patient friendly. The present study is a scoping review of the N400 and P600 ERP components in aphasia. To our knowledge, there has been no other review which specifically examines N400 and P600 within this patient population. The aim of this early exploratory study was to reveal patterns in the existing literature (for both the N400 and P600 as they relate to people with aphasia). It is hoped that future discussions arising from this review will direct muchneeded research in the development of clinically relevant ERPs for ongoing management of people with aphasia.

2. Methods

A scoping review was conducted to systematically map the research to date in the electrophysiology of aphasia. It sought to identify whether there is sufficient evidence in the literature to accept N400 and P600 as objective biomarkers in the diagnosis and recovery of aphasia. The findings of this review will support the development of a clinically applicable assessment tool, to be used by health professionals working with people with an acquired brain injury. The review also intends to identify any existing gaps in knowledge and highlight areas of further inquiry. The methodology for this scoping review corresponds to the methodology outlined by Tricco et al. (2018) for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Scoping Review Extension (PRISMA-ScR). This review protocol was developed a priori and is registered with the Open Science Framework.

2.1. Eligibility criteria

The eligibility criteria (see Table 1 for full selection criteria) was defined by the research team a priori, to answer the research question. To establish electrophysiological language processing markers, only those studies which examined the N400 and/or the P600 event-related potential components (ERPs) in a population of people with aphasia were included. Further to this, only studies which elicited these ERP components through a language paradigm were included. All publications included in this scoping review came from peer-reviewed journals between 1980 and December 2020 and were written in English.

2.2. Information sources

In order to identify all potentially relevant documents, the following electronic databases were searched: MEDLINE, Embase, Web of Science, Scopus, and PsycINFO. The searches for relevant literature were completed using the University of Auckland library portal for accessing online databases. The search strategies were guided through consultation with an experienced subject librarian. Search results were exported to an online reference management tool and duplicates were removed. Any additional relevant articles cited in eligible publications were identified via reference list searching. To ensure completeness a secondary search was completed in June 2021. No further articles which met the inclusion criteria were found.

All titles and abstracts of the publications yielded in the search were screened against the eligibility criteria by the first and second author. Any uncertainties of whether a publication met inclusion criteria were discussed by all authors and any disagreements were adjudicated by a third party prior to beginning data extraction. Both authors read the full text of all publications returned from the search which were deemed eligible for inclusion. Any queries about the selection of the studies were resolved through discussion. In the event of continued discrepancies, an unbiased third party was asked to adjudicate.

The requisite data from each included study was extracted by the first author. The second author verified the completeness and accuracy of the data extraction process. In instances where discrepancies arose, consensus was met through discussion or by further arbitration by the third author. Data were charted using a standardised data extraction form developed for this study. Extracted data included study design, participant characteristics, ERP characteristics, language paradigm used in the study, as well as the type and modality of stimuli used.

2.3. Data analysis

The selected studies were evaluated using a critical review form adapted from the McMaster University Occupational Therapy Evidence-Based Practice Research Group for quantitative studies (Law et al., 1998). Guidelines provided by Law et al., (1998) stipulate how to use the tool to evaluate each component of the studies under review. We closely adhered to the guidelines when calculating the quality of each study and awarding scores (out of 28). Each question was assigned a value of two for 'yes' and zero for 'no' or 'not addressed'. Studies were given a score of one when the question was not applicable to their study. Studies were evaluated on: (1) the study purpose and inclusion of appropriate background literature; (2) sample; (3) outcome measures; (4) description of the EEG methodology used; (5) reporting of results, including dropouts and exclusions; and (6) conclusion and clinical applicability. The design of the study was recorded but was not assigned a score. Studies were evaluated by the first two authors independently and any differences in scores were discussed until a consensus was reached.

Table 1
Inclusion and exclusion criteria for studies in the scoping review.

b	Inclusion Criteria	Exclusion Criteria
Participants	Adults (≥18 years)	Children (≤18 years)
	Men and Women	Bi- or multilingual
	Diagnosis of aphasia	Co-morbid speech and language difficulties
	Aphasia as primary neurological condition	Significant cognitive or memory impairments
	Acquired aphasia as a result of a brain injury	
Intervention	None	Surgical or pharmacological therapies
	Speech and language therapy	
Study parameters	Measurement of N400 and/or P600 components	No measurement of N400 or P600
	Linguistic stimuli	
Imaging techniques	EEG (Event-Related Potential)	fMRI[i], PET[ii], SPECT[iii], DTI[iv], MEG[v]
Publication type	Peer-reviewed articles	Books, poster, editorials, reviews, conference proceedings
Publication dates	1980–2021	Anything before 1980
Publication language	English	Other languages

[i] Functional Magnetic Resonance Imaging.
[ii] Positron emission tomography.
[iii] Single-photon emission computed tomography.
[iv] Diffusion Tensor Imaging.
[v] Magnetoencephalography.

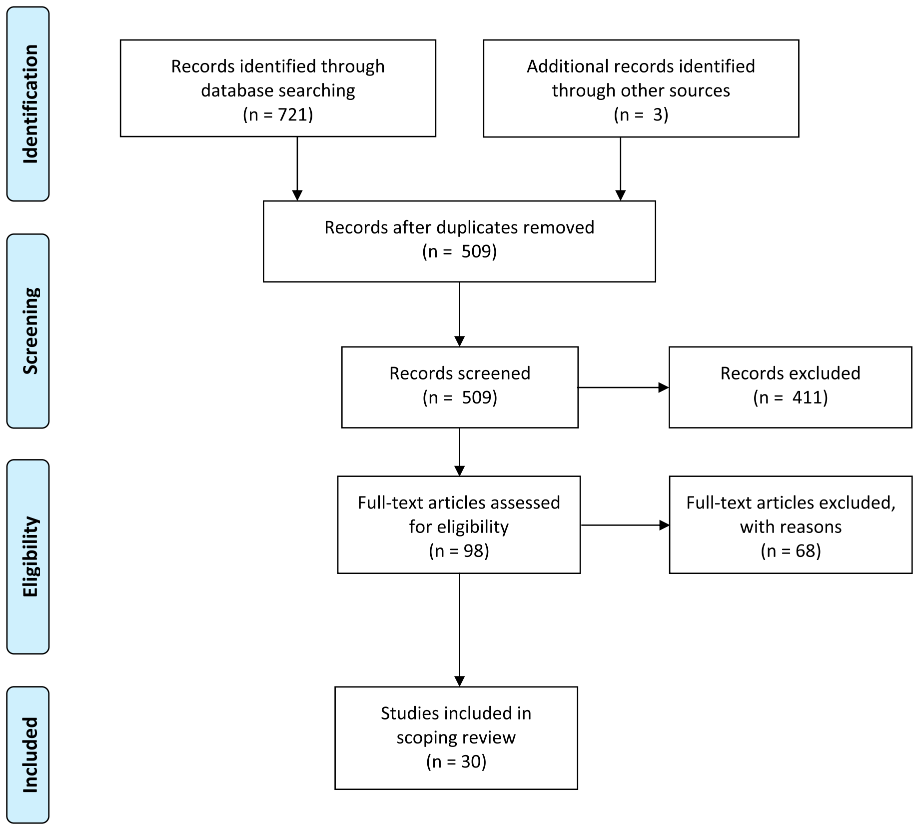

Fig. 1. PRISMA flow chart showing each step of the process to identify and select relevant articles.

3. Results

3.1. Sources

As seen in the PRISMA chart (Fig. 1) 721 articles were identified through searches of the electronic databases and review of article references with an additional three identified through other sources. After the removal of 215 duplicates, 509 articles remained, and the title and abstract were screened. Based on this screening, 411 were excluded, with 98 full articles subjected to full evaluation. Of these, 68 articles were excluded due to the following reasons: 32 did not focus on ERP components of interest, 22 for methodological reasons, seven did not include people with aphasia, two were not in English, and one involved the use of pharmacological intervention. A further two were excluded because they were unpublished theses and two more were excluded as the full text was unable to be retrieved. The remaining 30 studies were eligible for inclusion in this review. The 30 studies reviewed herein are presented in chronological order in Tables 2a, 2b, 2c, 2d.

While all the articles reported their findings in English, this was not the only language in which the studies were conducted. As seen in Fig. 2, nearly all studies used a language from the Indo-European language family, with most studies using a language in the Germanic language family. Eleven of the 30 articles (36%) were carried out in Dutch, followed by English (26%), and German (20%). Three of the studies were carried out in a language from East Asia, Japanese (7%) and Chinese (3%).

The team producing the research was also of interest to this scoping review. One research team was clearly dominant, with nine of the 30 articles (30%) coming from Hagoort and colleagues. Work produced by Friederici and associates was the next most prominent in the reviewed articles, with four studies (13%). The only other research team to appear more than once was Barwood and colleagues, who had two studies included in this review (7%).

3.2. Research design

3.2.1. Participant characteristics

In total, this review includes 778 participants. However, of these 778 participants only 344 are people with aphasia, with the remaining 434 participants acting as control participants. Through further analysis, it became evident there was a degree of participant recycling across the studies. This refers to studies using the same participants in a number of different studies, or where the authors produced numerous articles from a single sample. While this is not an uncommon practice, it can be misleading when reporting on findings within a certain population. A total of 344 people with aphasia are reported as participants in the studies included, however, when accounting for participant recycling this number drops to 237 people with aphasia.

Within the population of people with aphasia there was a clear dominance of people with non-fluent aphasia (53.5%) participating in over half of the ERP research included in the review. Second to this group are people with anomic aphasia (14%) followed by people with other non-specified fluent aphasia (11.7%). The smallest group of individuals represented in ERP aphasia research are those with conduction aphasia (1.2%). A number of studies either reported no specific, a non-classifiable, or a vague residual aphasia in some of their participants (8.7%) and a small number of studies reported a small portion of their participants as being "recovered" or "within normal limits" (4.7%). These percentages are shown in Fig. 3. In regard to control subjects, of the 434 total controls, the majority were healthy, neurotypical individuals. The remaining

Table 2a
Articles which focused on people with aphasia compared to normal controls.

Authors	People with aphasia	Actual people with aphasia[i]	Controls	Task[ii]	Modality[iii]	Stimuli	ERP[iv]	Quality score[v]
Revonsuo and Laine (1996)	1	1	17	PL	A	Sentences	N400	18
Friederici et al. (1998)	2	2	8	AC	A	Sentences	N400 + P600	21
ter Keurs et al. (1999)	16	11	23	PL	V	Sentences	N400	22
Connolly et al. (1999)	1	1	13	PL	A V	Sentences	N400	17
Cobianchi and Giaquinto (2000)	2	2	18	OD	A	Single words	N400	11
ter Keurs et al. (2002)	13	6	20	RE	V	Single words	N400	20
Hagoort et al. (2003a,b)	10	0	12	PL	A	Sentences	N400 + P600	22
Wassenaar and Hagoort (2005)	11	5	24	RE	V	Sentences	N400 + P600	24
Wassenaar and Hagoort (2007)	10	2	23	SR	A V	Sentences + Pictures	N400 + P600	24
Justus et al. (2011)	11	11	11	AC	A	Single words	N400	22
Kielar et al. (2012)	15	15	NS	SR	A V	Single words + Pictures	N400 + P600	26
Räling et al. (2016)	9	9	28	SR	A	Single words	N400	22
Robson et al. (2017)	8	8	10	SR	A V	Single words + Pictures	N400	18
Khachatryan et al. (2017)	15	15	32	AC	V	Sentences	N400 + P600	28

[i] Participants who have not appeared in another study included in this review.
[ii] PL = Passive Listening, AC = Acceptability, OD = Oddball, RE = Passive Reading, SR = Semantic Relatedness.
[iii] A = Auditory, V = Visual.
[iv] = Event-Related Potential.
[v] = McMaster Quality Score from Law, et al. (1998).

Table 2b
Articles which focused on people with aphasia based on severity.

Authors	People with aphasia	Actual people with aphasia[i]	Controls	Task[ii]	Modality[iii]	Stimuli	ERP[iv]	Quality score[v]
Hagoort et al. (1996)	20	20	20	PL	A	Single words	N400	26
Swaab et al. (1997)	14	4	18	PL	A	Sentences	N400	24
Swaab et al. (1998)	12	4	12	PL	A	Sentences	N400	26
Kitade et al. (1999)	30	30	23	OD	V	Single words	N400	20
Kojima and Kaga (2003)	10	10	10	SR	A	Single words	N400	22
Wassenaar et al. (2004)	10	0	17	PL	A	Sentences	P600	22
Kawhol et al. (2010)	20	20	NS	RE	V	Sentences	N400 + P600	24
Chang et al. (2016)	14	14	23	PR	V	Sentences	N400	26
Sheppard et al. (2017)	15	15	20	AC	A	Sentences	N400 + P600	24

[i] Participants who have not appeared in another study included in this review.
[ii] PL = Passive Listening, AC = Acceptability, OD = Oddball, RE = Passive Reading, SR = Semantic Relatedness.
[iii] A = Auditory, V = Visual.
[iv] = Event-Related Potential.
[v] = McMaster Quality Score from Law, et al. (1998).

Table 2c
Articles which focused on people with aphasia and speech language therapy.

Authors	People with aphasia	Actual people with aphasia[i]	Controls	Task[ii]	Modality[iii]	Stimuli	ERP[iv]	Quality score[v]
Barwood et al. (2011)	12	12	0	SR	V	Single word + picture	N400	26
Wilson et al. (2012)	15	15	NS	SR	V + A	Single word + picture	N400	18
Barwood et al. (2012)	12	0	0	SR	V	Single word + picture	N400	24
Aerts et al. (2015)	1	1	0	PL	A	Single words	N400	23

[i] Participants who have not appeared in another study included in this review.
[ii] PL = Passive Listening, AC = Acceptability, OD = Oddball, RE = Passive Reading, SR = Semantic Relatedness.
[iii] A = Auditory, V = Visual.
[iv] = Event-Related Potential.
[v] = McMaster Quality Score from Law, et al. (1998).

minority comprised non-linguistic neurologically impaired individuals.

3.2.2. Task paradigms

Linguistic-based decision paradigms were the most commonly employed task across all included studies, accounting for over half of the included studies (53%). Linguistic-based decision tasks involve presenting participants with a linguistic stimulus, either auditorily or visually, and recording their response (e.g. via button press). Of the 16 studies which used a linguistic-based decision task, acceptability tasks were most prevalent (50%). These required a decision to be made on the acceptability or appropriateness of a sentence. Only one linguistic decision task involved decisions around non-words (6%), whereas 44% required participants to judge the semantic relatedness of the stimuli, or to make a decision based on whether two stimuli matched. After linguistic decision

Table 2d
Articles which focused on people with aphasia and lesion location.

Authors	People with aphasia	Actual people with aphasia[i]	Controls	Task[ii]	Modality[iii]	Stimuli	ERP[iv]	Quality score[v]
Friederici et al. (1999)	7	7	14	AC	A	Sentences	N400 + P600	20
Frisch et al. (2003)	14	10	0	AC	A	Sentences	P600	18
Kotz et al. (2003)	14	0	0	AC	A	Sentences	N400 + P600	22

[i] Participants who have not appeared in another study included in this review.
[ii] PL = Passive Listening, AC = Acceptability, OD = Oddball, RE = Passive Reading, SR = Semantic Relatedness.
[iii] A = Auditory, V = Visual.
[iv] = Event-Related Potential.
[v] = McMaster Quality Score from Law, et al. (1998).

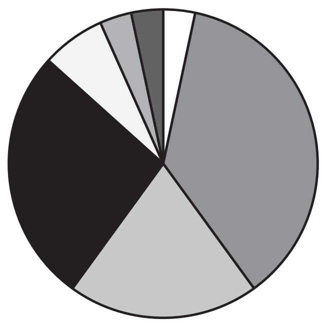

Fig. 2. Pie chart showing the most used languages in aphasia N400 and P600 Event Related Potential research.

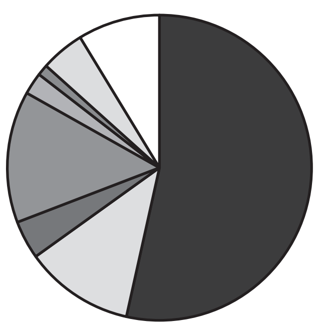

Fig. 3. Pie chart showing the various subtypes of aphasia participating in the studies.

tasks, passive tasks were the next most utilised paradigm (46%). These tasks are low-demand and require participants to read (21%) or listen (65%) to a stimulus with no additional tasks asked of them. Two of these passive studies included using an oddball paradigm (14%), a task characterised by the presentation of a deviant stimulus in a string of standard stimuli. One study used a visual oddball task requiring a response when the participant read the deviant word, and the other had a similar scenario but presented the words auditorily. One study did not specify the task in enough detail.

3.2.3. Modality

The modality in which the stimuli were presented was also explored in this review. In over half the studies (57%) stimuli were presented to participants solely via the auditory modality. This was by far the most common method of stimuli delivery. Studies which presented their stimuli solely though the visual modality accounted for 30% of the included studies. A small proportion of studies (13%) used both visual and auditory modalities for stimulus delivery. This most common involved an image being displayed on screen accompanied by either the congruent or incongruent label of the object depicted.

3.2.4. Stimuli

All stimuli used in the studies reviewed were linguistic in nature. However, they differed in the level of linguistic complexity. Over half (16) of the included studies (53.4%) used sentences as the stimuli to elicit ERP components, compared to eight studies (26.7%) which used single word stimuli. The processing of sentences is a more complex linguistic task compared to processing of single words. A small number of studies (16.7%) used both an image and a single word, whereas only one study used both pictures and sentences to elicit ERP components.

The average number of stimuli used across all studies was 258, with the most stimuli used in a single study being a mixture of 703 open- and closed-class words (330 and 373 respectively). The study with the smallest number of stimuli, and the only study to use fewer than one hundred stimuli, used 80 sentences which had differing levels of contextual predictability. One study did not provide detail about the number of stimuli used. The bulk of the studies (42%) used between 100–200 stimuli to elicit ERP responses (M = 144.5). The mid-range, 200–300 (M = 248.6), was used by 29% of studies, and then the high range, 300–400 (M = 328), by 11% of studies. A number of studies (18%) used more than 400 stimuli to elicit an ERP response.

3.3. Event-related potentials

A number of the studies examined a variety of ERPs including the N400 and P600 during their experiments. However, as they are not the focus of this review they will not be discussed here. Of the 30 studies included in this review, 28 (93%) investigated the N400 ERP component, either on its own or in conjunction with other ERPs. There were only two studies (1%) which solely examined the P600 response, with 10 of the studies (33%) investigating both the N400 and P600.

In reviewing the literature, it became clear that three separate approaches were most commonly utilised in aphasia ERP research. These were ERPs in people with aphasia compared to age-matched controls; ERPs in people with aphasia categorised by severity of deficit; and ERP responses in relation the effects of therapy. There were three studies which did not fall neatly into any of these categories, instead they examined ERP responses based on lesion location.

Fourteen of the 30 studies included in this review investigated how ERPs in people with aphasia differ from other control participant groups (Table 2a). This was by far the most common approach used in the literature, with the findings presenting a mixed bag of results. Just under half of these fourteen studies (43%) determined that people with aphasia have not lost access to lexico-semantic information. Rather, access to or integration of this information is incomplete or delayed compared to controls as evidenced by a delayed or absent N400. Regarding the P600, five of the six studies which examined P600 in people with aphasia, found it to also be significantly delayed or absent in people with aphasia compared to control participants. One study (Khachatryan et al., 2017) found the P600 to be larger and better defined in people with aphasia compared to older controls. Overall, the pattern of ERP responses in people with aphasia present a reduced amplitude, delayed latency and an unusual distribution when compared to control subjects.

A number of articles included in this review examined how the severity of aphasia impacts upon electrophysiological responses (Table 2b). Nine articles (Hagoort et al, 1996; Swaab et al. 1997; Swaab et al., 1998; Kitade et al., 1999; Kojima and Kaga, 2003; Wassenaar et al., 2004; Kawhol et al., 2010; Chang et al., 2016; Sheppard et al., 2017) categorised their participants into their level of comprehension based on the scores of standardised speech and language assessments. The results from these studies show that there is a clear differentiation in ERP profiles which appears to be correlated with the severity of aphasia. Participants categorised into the 'low' comprehension group were consistent in presenting with an ERP profile which significantly deviated in amplitude, latency and distribution. The 'high' comprehension group consistently showed ERPs which deviated from normal controls but did not reach statistical significance.

Only four of the 30 articles investigated ERP responses in relation to the effects of therapy (Table 2c). Two of them (Aerts, et al, 2015; Wilson et al. 2012) examined how intensive speech language therapy affected the N400 of people with aphasia. Wilson and colleagues found no changes in the amplitude of the N400 in people with aphasia post therapy, however the laterality shifted from right-sided to more left-lateralised. In contrast, Aerts and colleagues did find an increase in amplitude of the N400 in people with aphasia after early, intensive therapy. Improved behavioural and clinical measures were also found by both studies. The remaining two articles (Barwood, et al, 2011; Barwood et al, 2012) examined the effects of rTMS on people with aphasia post stroke. The studies both report on the findings of a single longitudinal study which demonstrated significant increases in the N400 deflection in people with aphasia who received rTMS compared to a placebo group. At the end of the study (12 months) the participants who received rTMS showed increased N400 responses and improved behavioural performances. None of the studies investigating therapy intervention examined the P600.

Three studies (Friederici et al., 1999; Frisch et al. 2003; Kotz et al. 2003) took a lesion approach to examining ERP in people with aphasia (Table 2d). All three articles were produced by the same research team. Two of the studies investigated participants with a lesion in the temporoparietal area compared to those with basal ganglia lesions. The findings revealed a double dissociation where participants with left temporoparietal lesions showed only a P600, whereas those with basal ganglia lesions showed no P600 response, but an extended negativity resembling the N400. The authors suggest these results are indicative of the basal ganglia modulating the P600, with a partial influence on the N400.

3.4. Study quality

All 30 studies were evaluated using an adapted version of the McMaster critical review form (Law et al., 1998). The results from this evaluation are presented in Fig. 4. Only one of the 30 studies received a maximum score of 28 (Khachatryan et al., 2017). A strength found across all papers was the outcome measures, with outcome measures being deemed reliable and valid in all studies except one (Connolly et al., 1999). For this scoping review, outcome measures were the ERPs N400 and P600. Studies were assigned points if the methodology was deemed appropriate to elicit a reliable and valid ERP response. This involved an examination of the type of stimuli used to elicit the ERPs, the task paradigm, and the time window used for analysis. The next strength in quality was the EEG methodology, where the majority of studies clearly outlined the methodological approach in a way which was replicable. Only two of the 30 papers (Revonsuo and Laine, 1996; Cobianchi and Giaquinto, 2000) were deemed to fall short in their methodological description.

A key area of study quality where many articles performed poorly was the conclusion and clinical applicability section. For this scoping review, a conclusion was determined as the authors succinctly stating how and why a research question had been answered, with clear implications for practice, policy, or further research. The term 'clinical applicability' was used to capture the applicability and transferability of findings into the real-world context. Studies were assigned points for detailing how the findings could be implemented within clinical practice by clinicians. Regarding their conclusion and clinical applicability, six of the 30 studies were assigned a full score, whereas seven of the 30 were assigned a score of zero because they lacked both a clear conclusion and clinical applicability. The six articles which were assigned a full score were also the only articles out of all 30 publications which addressed clinical applicability.

4. Discussion

In this scoping review 30 articles were identified which explored the relationship between aphasia and the N400 and P600 event-related potentials. The aim of the study was to determine whether these two ERPs are feasible candidates as potential diagnostic biomarkers in aphasia recovery. The literature concerning aphasia and these two evoked responses is relatively small. The studies which met inclusion criteria predominantly explored the N400 response, and did so through a wide range of approaches, with small sample sizes. However, across the studies reviewed, there is a level of consistency in the findings which gives strength to the feasibility of ERPs as a diagnostic tool, as well as directing future research.

The N400 has a long-standing association with both syntactic and semantic language processing. As deficits in the comprehension and expression of language are core features of aphasia, this ERP is a prime candidate for a neurophysiological biomarker. In support of this, most studies in the review found differences in the N400 characteristics of people with aphasia. Reduced or absent amplitudes, prolonged latency and irregular distribution across the scalp were all found in people with aphasia compared to healthy controls, as well as some other brain-damaged individuals. Furthermore, the studies which compared severity of aphasia consistently found significant differences between 'high' and 'low' comprehenders. Taken together, the results from the studies reviewed herein highlight that people with aphasia experience a disruption of semantic networks in language processing which is distinct from both non-brain damaged controls and individuals with brain damage not impacting the language centres.

Unlike the N400, the P600 response is more contentious. Divided opinion permeates the literature about what this ERP relates to. Traditionally, P600 was thought to index syntactic analysis and repair (Hagoort, 2003; 2008). However, a new line of inquiry posits that this ERP is reflective of integrated processes (Brouwer et al., 2012). Irrespective of these opposing views, the P600 does appear to have a relationship with language processing. There is markedly less research examining the P600 in people with aphasia, with only two studies investigating the P600 indepen-

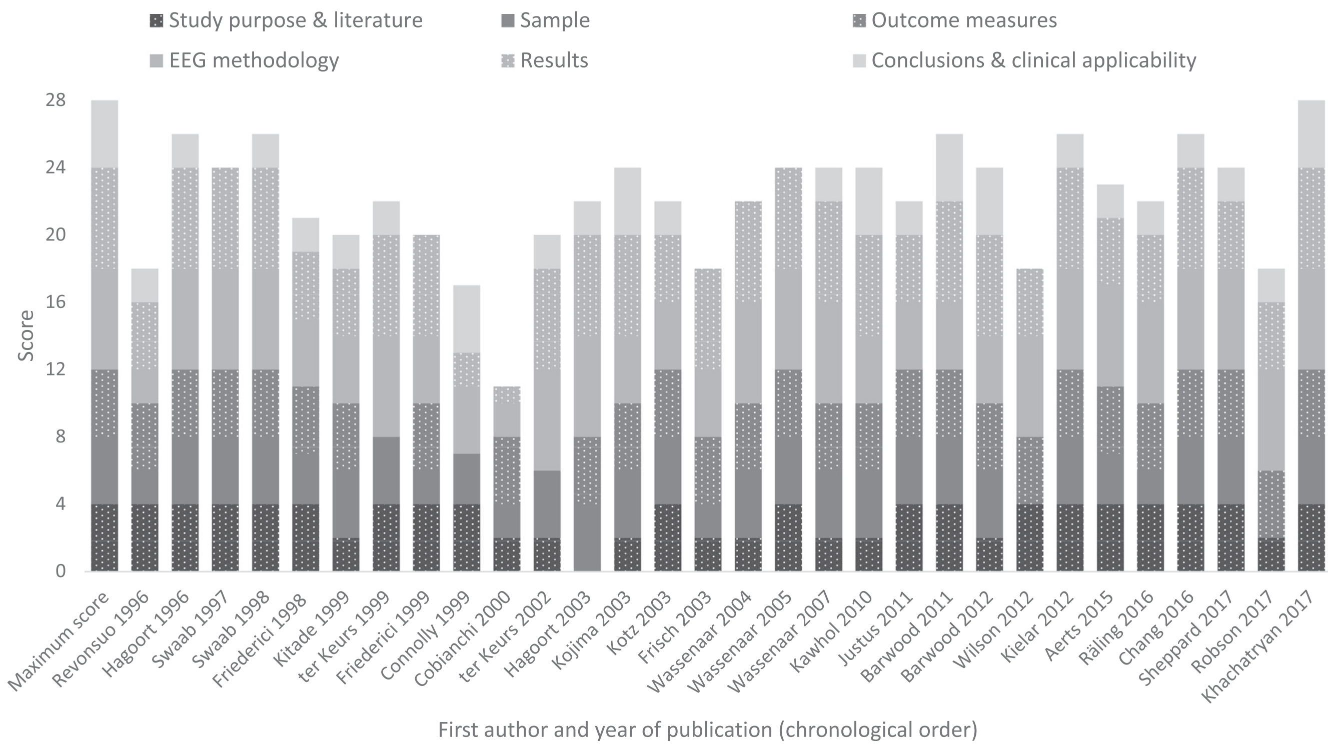

Fig. 4. Harvest plot of the McMaster quality scores allocated to included studies.

dently from the N400 (Frisch et al., 2003; Wassenaar et al., 2004). However, the findings in the limited literature show that people with aphasia demonstrate a different P600 profile in regard to amplitude and latency, compared to non-brain damaged controls. Similarly, one study (Wassenaar et al., 2004) showed that, like the N400, the P600 is correlated with severity of comprehension impairment.

While these results are encouraging in the prospect of neural biomarkers of language processing, there are some caveats in the findings which require further exploration. Amongst the studies included there was heterogeneity in the methodological approach, the stimuli, and the task paradigms. Although most studies utilised a linguistic-decision task, there was still a variety of approaches within those tasks, and while this in itself is not a problem, it does make comparing results more difficult. There was also significant heterogeneity in the number and classification of participants. In many studies, people with aphasia were treated as one uniform group, in spite of the classification of their aphasia, whereas other studies sought to include only specific subtypes of aphasia.

Further to the difficulties related to participant profiles, it became evident in this review that most of the research in this area is carried out with people with non-fluent aphasia (Broca's aphasia). This form of aphasia is often cited as an expressive difficulty which leaves comprehension relatively intact (Acharya and Wroten, 2021). There may be a number of explanations for this, however, a body of research primarily comprising people with non-fluent aphasia will largely skew the image of aphasia to favour profiles which align more closely to individuals with Broca's aphasia. A contributing factor to the abundance of participants with Broca's aphasia could also be the small number of researchers working in this area. Upon reviewing the articles included in this scoping review, it became clear that there are very few research groups producing most of the literature in this area. Further to this, there is a degree of participant recycling, where the same participants are being used in numerous experiments. This further narrows the profile of people with aphasia, which is largely heterogenous, to reflect the language processing of a small few.

The majority of studies reviewed in this scoping review were cohort studies (83%), with the remaining few being case studies (17%). The methodological quality of the studies varied between 11 and 28, out of a possible 28 (using the Law et al. (1998) critical review form) with the average score for study quality being 22. The quality component where most studies faltered was the conclusion and clinical applicability score. This was explained by most of the studies coming from a psychological sciences background. This suggests there is room for more clinically-driven studies into aphasia and ERPs. Upon reviewing the body of work included in this review, it is also apparent there is a lack of cohesion amongst the studies. While many of the studies made reference to the other work in this area, a large proportion of the studies approached similar aspects in differing ways. This has resulted in research in this area progressing laterally rather than moving forward in a unified manner.

Although the current body of literature is sparse and there are a number of inconsistencies between studies, the current scoping review has revealed some clear directions for future inquiry into ERPs and people with aphasia. These include a more targeted and uniform protocol for collecting and interpreting N400 and P600 data (particularly standardisation of paradigms and tasks), consideration of the subtypes of aphasia recruited for the research, and more consistency in ERP methodology. Furthermore, this scoping review has revealed inconsistencies in the reporting of normative data which provides a challenge to interpreting ERPs within real-world clinical settings. Developing a more robust normative dataset for a wide range of people with aphasia (including subtype, severity level, age, and gender) is likely to enhance the efficacy of ERPs as a clinical tool.

Additional future directions include reducing the gap between ERPs and clinical settings. To develop a feasible ERP clinical tool, collaboration between researchers and clinicians (such as a SLP) is essential. The insight provided by practising clinicians during the development phase is crucial to achieving an applicable tool outside of the research realm. Similarly, steps towards improving a clinician's understanding of ERPs would provide them with the skills and knowledge needed to actively engage with the research.

5. Conclusions

A total of 30 articles were reviewed to determine the feasibility of N400 and P600 as possible neural biomarkers in aphasia diagnosis and rehabilitation. The studies highlighted overall patterns of a reduced amplitude, delayed latency and different distribution in people with aphasia compared to controls, and that ERPs are modulated by severity of aphasia. A number of gaps in the literature were also identified; these include small and repetitive sample sizes, varied paradigms utilised, and differing modalities and types of stimuli. This scoping review has unearthed several areas for future research. One key area to address moving forward is the diversification of aphasia types participating in ERP research. Another is improving consistency within ERP methodology, to create a more reliable and valid clinical assessment based on a cohesive body of research. Overall, despite the limitations identified, the body of literature showed overall patterns that ERP profiles of people with aphasia do deviate from normal controls and are modulated by severity. This is a promising indication that ERPs could be feasible in a clinical setting as a diagnostic tool.

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CRediT authorship contribution statement

Ryan Meechan: Conceptualization, Data curation, Writing – original draft. **Clare McCann:** Data curation, Supervision, Writing – review & editing. **Suzanne Purdy:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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