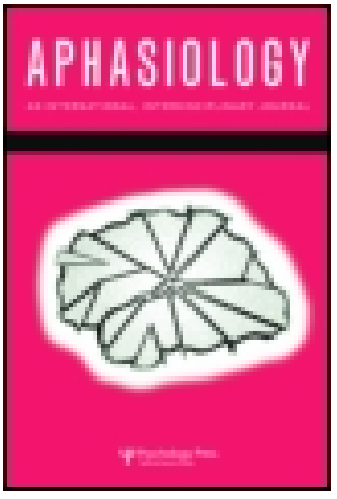

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Annelies Aerts[a], Katja Batens[bc], Patrick Santens[ad], Pieter Van Mierlo[e], Eline Huysman[f], Robert Hartsuiker[g], Dimitri Hemelsoet[d], Wouter Duyck[g], Robrecht Raedt[ad], Dirk Van Roost[h] & Miet De Letter[df]

[a] Department of Internal Medicine, Ghent University, Ghent, Belgium

[b] Department of Neurology, Institute of Neuroscience, Ghent University Hospital, Ghent, Belgium

[c] Department of Physical Therapy and Motor Rehabilitation, Ghent University Hospital, Ghent, Belgium

[d] Department of Neurology, Ghent University Hospital, Ghent, Belgium

[e] Department of Electronics and Information Systems, Ghent University – iMinds Medical IT Department, Ghent, Belgium

[f] Department of Speech, Language and Hearing Sciences, Ghent University, Ghent, Belgium

[g] Department of Experimental Psychology, Ghent University, Ghent, Belgium

[h] Department of Neurosurgery, Ghent University Hospital, Ghent, Belgium

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Aphasia therapy early after stroke: behavioural and neurophysiological changes in the acute and post-acute phases

Annelies Aerts[a]†, Katja Batens[b,c]*†, Patrick Santens[a,d], Pieter Van Mierlo[e], Eline Huysman[f], Robert Hartsuiker[g], Dimitri Hemelsoet[d], Wouter Duyck[g], Robrecht Raedt[a,d], Dirk Van Roost[h] and Miet De Letter[d,f]

[a]*Department of Internal Medicine, Ghent University, Ghent, Belgium;* [b]*Department of Neurology, Institute of Neuroscience, Ghent University Hospital, Ghent, Belgium;* [c]*Department of Physical Therapy and Motor Rehabilitation, Ghent University Hospital, Ghent, Belgium;* [d]*Department of Neurology, Ghent University Hospital, Ghent, Belgium;* [e]*Department of Electronics and Information Systems, Ghent University – iMinds Medical IT Department, Ghent, Belgium;* [f]*Department of Speech, Language and Hearing Sciences, Ghent University, Ghent, Belgium;* [g]*Department of Experimental Psychology, Ghent University, Ghent, Belgium;* [h]*Department of Neurosurgery, Ghent University Hospital, Ghent, Belgium*

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Background: There is reasonable evidence to suggest that speech and language therapy can be effective in the chronic stages of stroke recovery. However, the active ingredients remain unknown and several variables can influence therapy outcome, such as content, type, and amount of therapy. Neurophysiological measures, event-related brain potentials such as the N400 and P300, have shown to be sensitive markers of therapeutic effects. As a supplement to the usual behavioural evaluation methods, neurophysiological measures might help to further disentangle the effect of content, type, and/or amount of therapy.
Aims: The present single case study aims to investigate the effect of language therapy by combining behavioural and neurophysiological outcome measures in a patient with aphasia during the acute and post-acute stage after stroke. By further subdividing the therapy period into different therapy blocks, possible influences of content, type, and/or amount of therapy are investigated.
Methods & Procedures: RL is a 47-year-old man with a moderate non-fluent aphasia, who received three periods of therapy in the first four months after his stroke. The initial evaluation moment occurred 10 days post-stroke. First, he received an intensive language treatment of 30 hr in 3 weeks, which was followed by a conventional treatment of 30 hr in 7 weeks. Then, RL received a second, intensive language therapy of 30 hr in 3 weeks. This was followed by a period of 6 months without any form of language treatment. Behavioural and neurophysiological measures were collected after every therapy and therapy-free period. The effect of therapy was examined by comparing the whole therapy period with the therapy-free period, without differentiating between the intensive and conventional treatment. In a second analysis, a comparison was made between the intensive therapy periods and the conventional therapy programme.
Outcomes & Results: RL showed a general improvement on both behavioural and neurophysiological measures after the whole therapy period, which was preserved throughout the therapy-free period. Intensive treatment yielded better language outcomes as indicated by a behavioural and neurophysiological improvement in contrast with the behavioural deterioration of auditory discrimination of pseudowords and decline of the N400 neurophysiological marker, after the conventional therapy.

*Corresponding author. Email: katja.batens@uzgent.be
†Authorship is shared equally.

Conclusions: The present study demonstrates the outcome of early language treatment after stroke in which intensity can play an important role. In addition, the use of neurophysiological outcome measures provides added value to the behavioural evaluations in the context of therapeutic follow-up.

Keywords: intensity; aphasia therapy; neurophysiology; acute stroke; case study

Introduction

Aphasia is one of the most common symptoms following stroke. It affects one or more language modalities (expressive and/or receptive) and occurs in approximately 30–45% of all stroke patients (Dickey et al., 2010; Kauhanen et al., 2000). Evidence for the effectiveness of language therapy in post-stroke aphasia remains rather ambiguous. Language therapy might have some effect with respect to functional communication (therapy vs. no therapy), especially in the chronic stage of recovery (Allen, Mehta, McClure, & Teasell, 2012; Robey, 1998), yet no consensus has been reached about the treatment variables that contribute the most to language improvement (Brady, Kelly, Godwin, & Enderby, 2012).

Effects of content and type of therapy naturally cohere, as an impairment-oriented therapy will usually target certain aspects of language that are affected in patients with aphasia. For instance, training of sublexical phonological decoding and encoding embedded in an impairment-based treatment can induce an improvement of disturbed phonological processing capacities in a patient with chronic aphasia (Corsten, Mende, Cholewa, & Huber, 2007). Different types of outcome measures can also influence interpretation of language improvement. Impairment-specific measures can differentiate between phonological and semantic treatment, provided between 3 and 12 months post-stroke, in contrast to more general, functional outcome measures (Doesborgh et al., 2004; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014). Moreover, de Jong-Hagelstein et al. (2011) demonstrated that an impairment-specific, semantic, or phonological outcome measure can differentiate between communicative treatment and impairment-based, semantic, or phonological treatment in favour of the latter. This is an important issue to be taken into account when interpreting results from therapy studies.

In terms of timing of therapy after stroke, language treatment seems to improve communication outcome in people with moderate to severe aphasia in both very early and chronic stages of recovery from stroke, independent of type and content of treatment (Allen et al., 2012; Corsten et al., 2007; Godecke, Hird, Lalor, Rai, & Phillips, 2012; Godecke et al., 2013). However, others have suggested that aphasia therapy might not provide added value in the acute stage, as functional communication sometimes improves equally after speech and language therapy, with regular social contacts or even without therapy (Bowen et al., 2012; Laska, Kahan, Hellblom, Murray, & von Arbin, 2011).

The role of intensity (frequency and duration) of therapy has recently been postulated to be a predictive factor for aphasia recovery (Godecke et al., 2013). As treatment intensity increases, therapy outcome seems to improve (Cherney, Patterson, Raymer, Frymark, & Schooling, 2008). Based on a review by Bhogal, Teasell, and Speechley (2003), encompassing studies in both the acute and chronic post-stroke stage, more hours over a short period (massed practice; 8.8 hr per week for 11.2 weeks) shows more benefit than less hours over a longer period (2 hr per week for 22.9 weeks). When applying the principle of massed practice, patients with both acute and chronic aphasia can show a general improvement of their language abilities (e.g., Code, Torney, Gildea-Howardine, & Willmes, 2010; Meinzer, Streiftau, & Rockstroh, 2007; Pulvermuller et al., 2001). In these studies, improvements are mostly reported with respect to word retrieval and sentence

production, though there are studies that have reported improvement on auditory comprehension as well (Goral & Kempler, 2009; Szaflarski et al., 2008; Wilson et al., 2012). Intensity has also been investigated in the context of intensive comprehensive aphasia programmes (ICAPs) (Rose, Cherney, & Worrall, 2013). These programmes, entailing different treatment approaches (cognitive-linguistic, compensatory, social participation) provided at least 3 hr daily, can lead to improved communication and enhance life participation in individuals with aphasia in either the acute or chronic stage of recovery (Persad, Wozniak, & Kostopoulos, 2013; Rodriguez et al., 2013; Winans-Mitrik et al., 2014). Intensive therapy appears to provide long-term stability of improved language performance (Meinzer, Djundja, Barthel, Elbert, & Rockstroh, 2005), even in the acute stage after stroke (Kirmess & Maher, 2010). In light of investigating effects of intensity, it remains difficult to isolate this factor from other methodological factors, considering that it is recommended to adjust the type of therapy and the content of an impairment-based therapy to the nature of a patient's language impairment (Kendall et al., 2006). Nevertheless, the combination of high-intensity and impairment-based therapy seems to result in a language improvement in both acute and chronic stages of stroke.

Therapeutic outcome can also be affected by secondary neuronal plasticity phenomena that initiate immediately after a left hemisphere stroke (Saur et al., 2006). This can occur in the form of restitution of damaged, premorbid language regions, recruitment of perilesional areas directly surrounding the damaged area, or activation of homotopic language areas in the right hemisphere (Breier et al., 2004; Tyler, Wright, Randall, Marslen-Wilson, & Stamatakis, 2010). Saur et al. (2006) postulated a model of language recovery in terms of time post-stroke proceeding in three phases: days after stroke, mild left hemisphere activation co-occurs with a minimum of language recovery. Weeks after stroke, a significant increase in right hemisphere activation co-occurs with substantial improvement of language functions. Finally, months and years after stroke, a "re-shift" to the left hemisphere with a concomitant decrease of right hemisphere activation is related to further progression of language improvement. An important characteristic of neurons is the ability to form new connections and the more frequent neurons are active simultaneously, the stronger their connections become (Hebbian learning) (Kleim & Jones, 2008; Pulvermüller & Berthier, 2008). By increasing the intensity of impairment-based treatment, enhancement of neuronal connections can be achieved in the preferred left hemispheric lesional and perilesional areas in both the acute and chronic stage of stroke, and this has been related to a favourable outcome (Belin et al., 1996; Davis & Harrington, 2006; Fridriksson, Richardson, Fillmore, & Cai, 2012; Léger et al., 2002; Mattioli et al., 2014; Meinzer et al., 2004; Rochon et al., 2010).

Therapy-related differences in brain recovery and plasticity patterns can also be explored and monitored by means of neurophysiological measures. Event-related potentials (ERPs) have shown great potential in characterising, evaluating, and monitoring language abilities in patients with aphasia. The pre-attentive mismatch negativity (MMN) (Näätänen, Gaillard, & Mäntysalo, 1978), the attentive P300 potential (Sutton, Braren, Zubin, & John, 1965), and the N400 potential (Kutas & Hillyard, 1980) are very suitable to evaluate phonological and lexical-semantic input processes during the course of aphasia recovery (Becker & Reinvang, 2007; Csépe, Osman-Sági, Molnár, & Gósy, 2001; Kawohl et al., 2010), as an amplitude re-enhancement can be associated with improvement of language functions over time, throughout the different recovery phases (Ilvonen et al., 2003; Nolfe, Cobianchi, Mossuto-Agatiello, & Giaquinto, 2006; Pulvermuller, Mohr, & Lutzenberger, 2004). Surprisingly, ERP studies measuring therapeutic effects on language

abilities and its underlying reorganisation of neuronal circuits are scarce, and, to the best of our knowledge, to date have only been performed in patients with aphasia at least 1 year post-stroke. Nonetheless, the outcome is promising, demonstrating positive effects of intensive, impairment-based treatment in the form of increased amplitudes of P300 in response to meaningful words (Pulvermüller, Hauk, Zohsel, Neininger, & Mohr, 2005) or a shift from a more right-lateralised scalp distribution of the N400 before therapy to a more left-lateralised distribution after therapy (Wilson et al., 2012). In these studies, the neurophysiological changes were associated with an improvement in behavioural language performance. On the other hand, ERPs can also shed light on potential neuronal processing deficits despite intact behavioural performance (Becker & Reinvang, 2007). ERPs can provide a complementary instrument in the diagnostic and therapeutic evaluation of patients with aphasia and make it possible to connect neurological findings with clinical observations. This can not only support clinical practice but can enhance understanding of the neurophysiological mechanisms involved in language processing and its evolution after stroke (Kim & Tomaino, 2008). A long-term follow-up study of therapy effects, integrating clinical behavioural measures and neurophysiological recovery patterns, has not been presented in the literature until now. The development of neurophysiological normative data for phonological input processing (Aerts et al., 2013) offers the opportunity to field-test the clinical relevance of ERPs. The present single case study aims to investigate the effect of language therapy on behavioural and neurophysiological outcome measures during the acute and post-acute phase after stroke. For the present study, the acute phase entailed the first three months after stroke, the post-acute phase ranged from 4 months to 12 months after stroke, and the chronic phase started from 1 year after stroke (Robey, 1998). For the first analysis, a period of 105 days therapy in the (post) acute stage is compared with a period of 184 days without a targeted therapeutic language intervention in the post-acute stage. Additionally, it is tested whether the implementation of neurophysiological correlates can provide added value in the diagnostic and therapeutic language evaluation. For the second analysis, within the whole therapy period, a differentiation is made between three different therapy blocks, in which 3 weeks of intensive therapy (2 hr per day, 5 days a week), one in the acute and one in the post-acute stage, are compared with 7 weeks of conventional therapy (1 hr per day, 4 days a week) in the post-acute stage of stroke.

Method

Patient description

The patient under study (RL) is a Dutch-speaking, right-handed (tested with the methodology of Van Strien, 1992) physical trainer who suffered an ischaemic stroke at the age of 47. He had normal hearing and sight prior to his stroke, as confirmed by the annual medical controls within the scope of his professional activity. There was no history of neurological or psychiatric disorders or of speech or language (developmental) disorders prior to the stroke.

RL was acutely admitted to the stroke unit after sustaining a complex partial seizure, characterised by unresponsiveness and confusion. Subsequently, he was unable to speak or execute orders. Neuroimaging confirmed the presence of an ischaemic lesion in the left hemisphere, encompassing the caudate nucleus, the insula, the anterior tip of the superior temporal lobe, and the parietal cortex (see Figure 1). A first-language screening 1 day post-onset confirmed a clear picture of a non-fluent aphasia, with only a single word

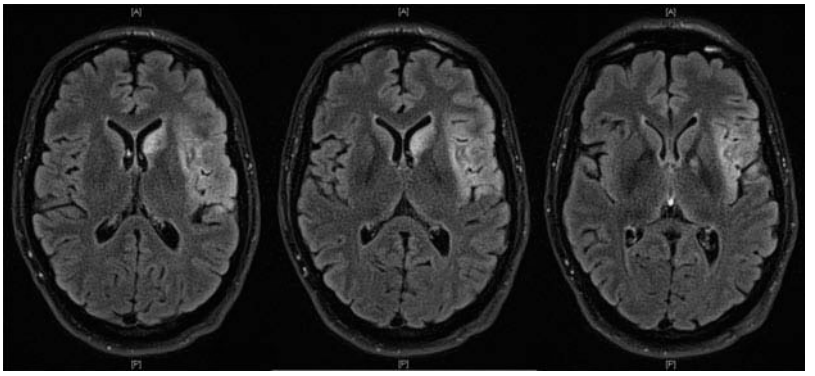

Figure 1. MRI scan 10 days post-stroke confirming the presence of an ischaemic lesion in the left hemisphere, encompassing the caudate nucleus, the insula, the anterior tip of the superior temporal lobe, and the parietal cortex.

expressed ("ja" ["yes"]), and with severely compromised auditory and reading comprehension. In addition, there were signs of orofacial apraxia (e.g., dissociation of voluntary oral movements vs. automatic oral movements and groping). There was no hemiparesis or hemisensory disorder. The language abilities of RL improved every day within the first week after stroke.

Study design

Behavioural and neurophysiological evaluations were performed in the course of the acute and post-acute phase (see Figure 2). After the initial evaluation moment (τ1), 10 days post-onset, RL was given a first block of 3 weeks of (intensive) therapy. The training programme consisted of 30 hr of therapy in a 3-week period. Each therapy session lasted 2 hr and was provided 5 days a week. After this therapy block, a second evaluation took place (τ2). Then, a second block of therapy entailed a conventional programme and provided the maximum amount of therapy hours per week as prescribed by the National Institute for Health and Disability Insurance in Belgium, which is 1 hr a day, 4 days a week. Given that the total amount of therapy hours in the conventional therapy needed to be the same as the intensive therapy block, 30 hr of therapy were provided over a 7-week period. A third evaluation occurred after the conventional therapy programme (τ3). After τ3, a third block of intensive therapy of again 3 weeks was implemented (2 hr per session, 5 days a week) and was followed by another evaluation moment (τ4). Finally, a 6-month period of no intervention was introduced, which was followed by a fifth evaluation

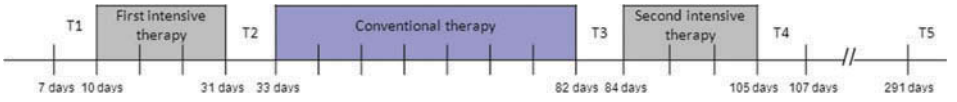

Figure 2. Timeline of all evaluation moments and therapy periods. [To view this figure in colour, please see the online version of this Journal.]
τ1 = initial evaluation moment; τ2 = evaluation after first intensive therapy; τ3 = evaluation after conventional therapy; τ4 = evaluation after second intensive therapy; τ5 = evaluation after therapy-free period.

moment (τ5). The first test period was spread over 3 days because it contained more tests, while all other evaluations were administered in 2 days. The evaluations were administered the days immediately before and after a therapy period. RL was capable of working on this high-intensity rate so early after stroke and was not hindered by headaches or extreme fatigue, which made him a suitable candidate for this study design.

Language assessment

Behavioural language evaluation

In order to obtain an overall objective impression of RL's post-stroke language abilities, the complete Dutch version of the Aachen Aphasia Test (AAT) (Graetz, De Bleser, & Willems, 2005) was administered. Although the early use of the AAT prevents us from comparing it with the normative data and the language status of the patient is instable, it provides an overall standardised summary of the language capacities of RL at the starting point of the whole therapy period.

Subsequently, five different subtests of the Dutch version of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Bastiaanse, Bosje, & Visch-Brink, 1995) were conducted: phoneme discrimination in pairs of pseudowords (PW) (PALPA 1), phoneme discrimination in minimal pairs of real words (RW) (PALPA 2), auditory lexical decision (PALPA 5), repetition of PW (PALPA 8), and verbal attention for digits (PALPA 12). Only the first column of PALPA 1 and PALPA 2 were administered, as allowed by the guidelines (Bastiaanse et al., 1995). The results of PALPA 1 and PALPA 2 were compared with normative data (N = 71) (Aerts, Santens, & De Letter, 2012, unpublished data).

Finally, two additional impairment-based language tests were conducted, only at the initial evaluation moment (τ1), without further implementation after the therapy blocks. The first test was the "Werkwoord en Zinnen Test" (WEZT), the Dutch version of "Verb and Sentence Test" (VAST) (Bastiaanse, Edwards, & Rispens, 2002). Only the four production tasks were administered, comprising naming of verbs, production of non-finite verbs in sentences, production of finite verbs in sentences, and construction of sentence anagrams. Second, the subtests "naming" and "verbal association" of the "Semantische Associatie Test", the Dutch version of "Semantic Association Test" (SAT), were conducted (Visch-Brink, Denes, & Stachowiak, 1993).

Neurophysiological language evaluation

The phonological input processing tasks explained later were previously investigated in a healthy control group in the context of developing neurophysiological normative data. The rationale behind the tasks, how they are matched with the PALPA tasks described earlier and what the ensuing ERP measures mean can be found in the paper describing the normative study (Aerts et al., 2013).

Paradigms and stimuli

Auditory phoneme discrimination. The first experiment (a phoneme discrimination task) consisted of three different auditory oddball paradigms both in a pre-attentive (MMN) and attentive (P300) condition. During the pre-attentive condition, RL was instructed to ignore the stimuli and to focus his attention on a silent movie. During the attentive condition, RL

pushed a button every time he heard the infrequent stimulus. Within the MMN and P300 paradigm, each block consisted of 750 stimuli and 150 stimuli, respectively. The standard phoneme was [bə] and the deviant phonemes were [gə] (covering PoA), [pə] (covering voicing), and [mə] (covering MoA). The stimuli were created in such a way that the standard and deviant stimulus only differed in one phonemic contrast. Stimuli were generated using the website NeXTeNS (Nederlandse Extensie voor Tekst naar Spraak) (http://nextens.uvt.nl/demo.htm; Marsi, Busser, Daelemans, Hoste, & Reynaert, 2002), where text could be converted to speech. In all stimulus blocks, the standard and deviant phoneme appeared with a probability of 0.80 and 0.20, respectively. The stimuli were given in a random order in which two deviants could not follow each other without having one standard in between. All the spoken phonemes had a duration of 150 ms. The interstimulus interval (ISI) was set to 500 ms in the MMN paradigm and 2000 ms in the P300 paradigm. The stimuli were presented binaurally between 60 and 70 dB sound pressure level (SPL) using Apple Inc. earphones placed directly in the external ear.

Auditory word recognition. The second experiment consisted of a word recognition task where PW were implemented as deviant stimuli and RW as standard stimuli. RL was instructed to ignore the stimuli and to focus his attention to a silent movie. The standard stimuli and deviant stimuli appeared with a probability of 0.80 and 0.20, respectively. A total of 125 stimuli were presented, including 100 RW (all nouns) and 25 PW. PW were derived from the RW by replacing one vowel and one consonant in 25 RW randomly selected from the list of 100 existing words. Stimuli were spoken by a 24-year-old female Dutch native speaker with a flat intonation and digitally recorded with a sampling frequency of 44.1 kHz. The stimuli were given in a random order, with the constraint that two PW could not follow each other without having one RW in between. The RW had a mean lexical frequency of 3.15 log10freq (*SD* = 0.39) (Keuleers, Brysbaert, & New, 2010), a mean age of acquisition of 6.0 years (*SD* = 1.21) (Ghyselinck, Custers, & Brysbaert, 2003), and the length was five phonemes in one or two syllables. The stimuli were presented with an ISI of 1000 ms and presented binaurally between 60 and 70 dB SPL using Apple Inc. earphones placed directly in the external ear.

Electroencephalogram (EEG): recording and analysis

The EEG (0.5–100 Hz band-pass, notch filter disabled) was recorded through 23 Ag/AgCl-electrodes using a linked ears reference and an electrode placed on the forehead as ground. Electrodes were placed on the scalp according to the international 10-20 system. The impedance of the electrodes was kept below 5 kΩ. Data were collected using a SynAmp (Neuroscan) amplifier and were continuously digitised at a 500 Hz sampling rate.

EEG analysis was performed using BrainVision Analyzer 2 (Brain Products, Munich, Germany). The EEG signal was filtered with a 0.5–30 Hz band-pass filter and notch filter enabled at 50 Hz. Using independent component analysis, artefacts caused by eye movements were removed by excluding two components (eye blinks and saccades) based on inspection of the components' topography. For the three P300 paradigms, the EEG was segmented into 1100-ms-long epochs from 100 ms pre-stimulus to 1000 ms post-stimulus. For the three phoneme discrimination MMN paradigms, the EEG was segmented into 500-ms-long epochs from 100 ms pre-stimulus to 400 ms post-stimulus. Finally, for the word recognition MMN paradigm, the EEG was segmented into 1000-ms-long epochs

from 100 ms pre-stimulus to 900 ms post-stimulus. The epochs were baseline corrected using a pre-stimulus window of 100 ms. All epochs containing data exceeding 100 μV were rejected for further analysis. The standard and deviant trials were averaged separately. Finally, to compute the MMN in the phoneme discrimination task, the average ERP of the standard trials was subtracted from the average ERP of the deviant trials. Peak detection was carried out semi-automatically at electrodes corresponding to normative data previously developed (Aerts et al., 2013). Peak latencies and peak amplitudes were measured in time windows determined by the averaged standard/deviant (P300; N400) and difference (MMN) waveform, which were different for every ERP. For phoneme discrimination, all MMNs were measured between 100 and 300 ms at Cz and Fz. All P300 s were analysed between 200 and 700 ms at Pz. For word recognition, the N400 was measured between 300 and 800 ms at Cz.

Therapeutic methodology

Therapy was conducted at the patient's house or at the speech therapist's office. The whole therapy period consisted of three well-defined blocks of impairment-based therapy. The first block of therapy ("first intensive therapy period"), starting 10 days post-stroke onset, consisted of an intensive, tailored therapy programme, which was composed based on the diagnostic results of both the neurolinguistic and neurophysiological tests. The language exercises focused on the enhancement of the connection between phonological auditory representations of words and their semantic content.

The second block of therapy ("conventional therapy period"), starting 33 days post-stroke onset, entailed a conventional programme, based on the neurolinguistic test results and the error pattern observed by the speech therapist. Auditory and visual phonological exercises at word and sentence level were combined with syntactically orientated assignments.

The third and final block of therapy ("second intensive therapy period"), starting 84 days post-stroke onset, was again an intensive therapy programme with the same amount of hours, frequency, and duration as the first intensive therapy period. Once again the content of the therapy was based on the neurolinguistic and neurophysiological results. The exercises focused on improving the sublexical processes. Finally, a therapy-free period of 6 months was incorporated, after which an additional assessment was administered to measure any effects of a period without extra language stimulation. This therapy-free period was incorporated in the programme at request of RL himself. All therapy sessions were given by two qualified speech and language pathologists (SLP) (authors KB and EH). KB gave all intensive therapy sessions (between τ1 and τ2 and between τ3 and τ4) and EH gave the conventional therapy sessions (between τ2 and τ3). All the diagnostic and post-therapy neurophysiological evaluations were conducted by a third SLP (author AA). To prevent methodological bias, both SLPs did not report about the therapy progress to each other or to author AA. No other language or cognitive therapies were allowed during the therapy periods.

Statistical analysis

Behavioural measures

The AAT results at τ2, τ3, τ4, and τ5 were analysed using the computer program for analysis of AAT score profiles by means of a χ^2 test ($p < .05$) (Graetz et al., 2005). The results of τ1 were only represented in a descriptive manner because no normative data

exist for AAT within 4 weeks after stroke. The same computer program was used to compare the AAT results of RL between evaluation moments, except the comparison with τ1 as previously explained. Effect sizes were calculated to estimate the magnitude of differences between the different test moments of all PALPA tasks. The effect size was classified as reported in the Robey, Schultz, Crawford, and Sinner (1999) review of single-subject research in aphasia, where 2.6, 3.9, and 5.8 correspond to small-, medium-, and large-sized effects, respectively.

Neurophysiological measures

First, neurophysiological outcome measures of RL were compared to neurophysiological normative data recently developed by our research group (Aerts et al., 2013). Peak latency and amplitude values were compared to normative values of RL's age group (40–49 years old) at every evaluation moment (τ1, τ2, τ3, τ4, and τ5) for every paradigm. Considering that the normative data are only developed for a limited number of electrodes (MMN: Fz and Cz; P300: Pz; N400: Cz), RL was compared to the norms only for these electrode sites. Effect sizes were calculated to estimate the magnitude of difference between the normative values and RL's values. Standardised mean difference (*d*) and the corresponding scale (0.2 equals a small effect, 0.5 a medium effect, and 0.8 a large effect) was used (Cohen, 1988) in concurrence with other neurophysiological research papers using effect sizes (Ferreira-Santos et al., 2012; Kwon et al., 2010).

Second, a comparison between evaluation moments was performed (τ1↔τ2, τ2↔τ3, τ3↔τ4; τ1↔τ4 and τ4↔τ5) at every electrode site to map potential brain reorganisation patterns. Recently, a new approach has been proposed, based on the non-parametric bootstrapping technique, and has proven to be a valuable and viable statistical method (Lin, Wu, Wu, Liu, & Gao, 2013; Oruç et al., 2011; Parker, 2006; Picton et al., 2000; Rousselet et al., 2009). The bootstrapping technique has already been shown to be sensitive enough for demonstrating the presence of the face-selective N170, feedback error-related negativity and P300 in healthy controls (Oruç et al., 2011), so it can provide a feasible and valuable tool in the clinical, therapeutic evaluation of individual patients with aphasia. Consequently, this approach was chosen to compare results at different evaluation moments.

For passive, pre-attentive phoneme discrimination (MMN), analysis was performed on the difference waveforms (deviant—standard), containing ±750 trials, in a fixed temporal window of 200 ms (100–300 ms) containing the MMN peak. For active, attentive phoneme discrimination (P300), analysis was performed on the deviant waveforms, containing ±30 trials, in a fixed temporal window of 500 ms (200–700 ms) containing the P300 peak. Finally, for passive, pre-attentive word recognition, analysis was performed for PW (25 trials) and RW (100 trials) separately with a focus on the N400 potential, evaluated in a fixed temporal window of 600 ms (300–900 ms). The difference between maximum amplitudes in the fixed temporal windows was taken to represent the contrast between evaluation moments (τ1↔τ2, τ2↔τ3, τ3↔τ4; τ1↔τ4 and τ4↔τ5). To test whether this contrast was significantly larger than zero (for a negative potential) or smaller than zero (for a positive potential), the bootstrap analysis was performed. Eventually, a histogram of contrast values obtained from 50,000 resampled data sets was constructed. The lower 5th percentile point of this histogram served as the critical value for (one-tailed, e.g., $\tau 1 < \tau 2$) significance at the 0.05 alpha value.

Results

Overall therapy effect (whole therapy period vs. therapy-free period)

Behavioural results

At the initial evaluation moment (τ1), RL revealed impairment on every subtest of the AAT. Of note were the phonological paraphasias that increased with word and sentence length during repetition, the near perfect (29/30) reading task, the inability to compose words and sentences (0/30), the perseveration when naming objects, the listing of the different elements in a situation picture instead of the formulation of a sentence, and the difficulties comprehending words with double meaning at word and sentence level. The spontaneous language production was characterised by slow speech rate, language automatisms, semantic and phonological paraphasias, and predominately single-word output. To talk about familiar topics, RL needed interlocutor assistance. On the PALPA assessments, RL reached maximum scores (36/36) on the behavioural phoneme discrimination tests (PALPA 1 and 2). There were deficits in the auditory lexical decision (PALPA 5; 145/160), which were caused by difficulties in recognising PW (RW 79/80; PW 66/80). The repetition of PW (24/30) revealed phonological paraphasias. Auditory verbal attention (PALPA 12) was severally impaired (25/60). The SAT revealed semantic disturbances indicated by a disruption of the subtests naming (15/30) and verbal association (21/30). The VAST indicated an impairment in naming of action verbs (15/30). RL perseverated strongly during this task, which was comparable with the naming of objects in the AAT (47/120). RL's error types were predominantly "no response" errors during the production of non-finite verbs in sentences (2/30) and production of finite verbs in sentences (3/10), which made it difficult to decide whether this was due to a morphosyntactic problem or a problem in word retrieval. In the construction of sentence anagrams (16/20), RL switched objects and subjects in passive sentences.

At the evaluation after the whole therapy period (τ4), AAT analyses indicated an overall improvement, which was largely accomplished within the first five weeks post-stroke. At τ4, all scores on the AAT subtest reached very high scores, although no maxima were obtained. In the spontaneous language production, some phonological paraphasias were still noted. RL reached the maximum score for phoneme discrimination (PALPA test 1 and 2), auditory lexical decision for RW (PALPA 5 RW), and repetition of PW (PALPA 8) after τ4. The auditory lexical decision for PW (PALPA 5 PW) improved moderately ($d = 4.85$) over the whole therapy period. Verbal attention (PALPA 12) was the only test that showed no improvement or deterioration ($d = 1.69$).

There were no changes on any of the behavioural tests at the evaluation after the therapy-free period (τ5). The results of the AAT and PALPA are summarised in Table 1. The differences in raw scores of the AAT together with the effect sizes of the PALPA results are summarised in Table 2.

Neurophysiological results

RL's ERP amplitudes and latencies of the MMN, P300, and N400 compared with neurophysiological normative data, as calculated with the Cohen's *d* effect size, are summarised in Table 3 for every evaluation moment. The topographical distribution of the amplitude and latency alterations after the whole therapy period (τ4) and therapy-free period (τ5) can be found in Table 4. A clear description of an interpretation of the electrode denomination is provided in the legend. The ERP waveforms of the N400 PW before and after the whole therapy (τ1, τ4) and after the therapy-free period (τ5) are represented in Figure 3.

Table 1. Overview of all behavioural test results of AAT and PALPA.

				IT	CT	IT	NT
AAT	Max		τ1	τ2	τ3	τ4	τ5
Spontaneous language production	30		16	25	27	28	30
Communicative behaviour	5		2	4	5	5	5
Articulation and prosody	5		3	4	5	5	5
Automatic language	5		3	5	5	5	5
Semantic structure	5		3	4	4	4	5
Phonological structure	5		4	4	4	4	5
Syntactic structure	5		1	4	4	5	5
Token test (severity score)	0		45	13	8	8	5
Repetition	150		107	146	148	147	148
Written production	90		44	87	88	88	87
Reading out loud	30		29	29	30	30	30
Compiling to dictation	30		0	29	29	29	29
Writing to dictation	30		15	29	29	29	28
Naming	120		47	111	117	115	115
Language comprehension	120		74	103	112	118	120
Auditory comprehension	60		35	46	56	58	60
Reading comprehension	60		39	57	56	60	60
PALPA	Max	*SD*	τ1	τ2	τ3	τ4	T5
1 phoneme discrimination—pseudowords	36	0.83	36	35	32	36	35
2 phoneme discrimination—minimal pairs	36	0.75	36	36	36	36	36
5 lexical decision—total	160	2.27	145	156	152	154	158
5 lexical decision—real words	80	0.88	79	80	78	80	80
5 lexical decision—pseudowords	80	1.81	66	76	73	74	78
8 repetition pseudowords	30	1.30	24	30	30	30	29
12 verbal attention: digit span	60	5.93	25	42	36	35	39

Notes: Max = maximum score; SD = standard deviation; τ1 = initial evaluation moment; τ2 = evaluation after the first intensive therapy period; τ3 = evaluation after the conventional therapy period; τ4 = evaluation after the second intensive therapy period; τ5 = evaluation after the therapy-free period; IT = intensive therapy period; CT = conventional therapy period; NT = no therapy.

Table 2. Effect sizes of the PALPA results between the different evaluation moments.

PALPA	τ1–τ2	τ2–τ3	τ3–τ4	τ1–τ4	τ4–τ5
1 phoneme discrimination—pseudowords	1.21	−3.64*	4.85**	0.00	−1.21
2 phoneme discrimination—minimal pairs	0.00	0.00	0.00	0.00	0.00
5 lexical decision—real words	1.14	−2.27	2.27	1.14	0.00
5 lexical decision—pseudowords	5.52**	−1.66	0.55	4.42**	2.21
8 Repetition pseudowords	4.62**	0.00	0.00	4.62**	0.00
12 Verbal attention: digit span	2.87*	−1.01	−0.17	1.69	0.67

Notes: Effect sizes of PALPA 1, 2, and 5 at all evaluation moments. * Small effect size > 2.60; ** medium effect size > 3.90; τ1 = initial evaluation moment; τ2 = evaluation after the first intensive therapy period; τ3 = evaluation after the conventional therapy period; τ4 = evaluation after the second intensive therapy period; τ5 = evaluation after the therapy-free period.

Auditory phoneme discrimination

At the initial evaluation moment (τ1), RL showed smaller amplitudes compared to the normative group for all phonemic contrasts (PoA, voicing, and MoA) in both the pre-

Table 3. Normative data (first column; Aerts et al., 2013) and RL's results for peak amplitudes and latencies at the five evaluation moments.

		Norm 40–49 years	τ1	τ2	τ3	τ4	τ5
Amplitude							
MMN (Fz+Cz)	PoA	*M* −3.22	*−1.23*	*−2.70*	*−2.58*	*−1.78*	*−0.99*
		SD 2.43	*d* = 0.82	*d* = 0.21	*d* = 0.26	*d* = 0.59	*d* = 0.92
	Voicing	*M* −2.73	*−0.06*	*−1.55*	*−1.97*	*−1.27*	*−1.16*
		SD 1.48	*d* = 1.80	*d* = 0.80	*d* = 0.51	*d* = 0.99	*d* = 1.06
	MoA	*M* −2.51	*−0.12*	*−1.35*	*−1.69*	*−0.55*	*0.04*
		SD 1.53	*d* = 1.56	*d* = 0.76	*d* = 0.54	*d* = 1.28	*d* = 1.61
P300(Pz)	PoA	*M* 13.09	*5.19*	*4.44*	*7.67*	*9.15*	*6.47*
		SD 4.00	*d* = 1.97	*d* = 2.16	*d* = 1.35	*d* = 0.98	*d* = 1.65
	Voicing	*M* 12.67	*3.75*	*2.86*	*9.62*	*7.60*	*4.75*
		SD 3.72	*d* = 2.40	*d* = 2.64	*d* = 0.82	*d* = 1.36	*d* = 2.13
	MoA	*M* 11.63	*3.90*	*7.98*	*10.54*	*4.75*	*5.54*
		SD 4.07	*d* = 1.90	*d* = 0.90	*d* = 0.27	*d* = 1.69	*d* = 1.50
N400(Cz)	RW	*M* −2.60	*−0.72*	*−2.58*	*−2.80*	*−1.16*	*−1.94*
		SD 1.17	*d* = 1.61	*d* = 0.02	*d* = −0.17	*d* = 1.23	*d* = 0.56
	PW	*M* −3.60	*−1.47*	*−4.22*	*1.15*	*−4.92*	*−3.06*
		SD 1.93	*d* = 1.10	*d* = −0.32	*d* = −2.46	*d* = −0.68	*d* = 0.28
Latency							
MMN(Fz+Cz)	PoA	*M* 171	*120*	*134*	*232*	*146*	*144*
		SD 27.28	*d* = 1.87	*d* = 1.36	*d* = −2.24	*d* = 0.92	*d* = 0.99
	Voicing	*M* 164	*206*	*287*	*211*	*191*	*156*
		SD 37.95	*d* = −1.11	*d* = −3.24	*d* = −1.24	*d* = −0.71	*d* = 0.21
	MoA	*M* 174	*145*	*143*	*156*	*184*	*158*
		SD 28.47	*d* = 1.02	*d* = 1.09	*d* = 0.63	*d* = −0.35	*d* = 0.56
P300(Pz)	PoA	*M* 403	*346*	*492*	*440*	*420*	*322*
		SD 60.04	*d* = 0.95	*d* = −1.48	*d* = −0.62	*d* = −0.28	*d* = 1.35
	Voicing	*M* 396	*466*	*402*	*506*	*394*	*464*
		SD 47.99	*d* = −1.46	*d* = −0.12	*d* = −2.29	*d* = 0.04	*d* = −1.42
	MoA	*M* 376	*446*	*410*	*432*	*394*	*424*
		SD 33.51	*d* = −2.09	*d* = −1.01	*d* = −1.67	*d* = −0.54	*d* = −1.43
N400(Cz)	RW	*M* 504	*490*	*480*	*602*	*554*	*404*
		SD 61.86	*d* = 0.23	*d* = 0.39	*d* = −1.58	*d* = −0.81	*d* = 1.62
	PW	*M* 496	*624*	*560*	*594*	*606*	*472*
		SD 53.61	*d* = −2.39	*d* = −1.19	*d* = −1.83	*d* = −2.05	*d* = 0.45

Notes: Electrode of interest is denoted in the table. PoA = place of articulation; MoA = manner of articulation; RW = real words; PW = pseudowords; τ1 = initial evaluation moment; τ2 = evaluation after the first intensive therapy period; τ3 = evaluation after the conventional therapy period; τ4 = evaluation after the second intensive therapy period; τ5 = evaluation after the therapy-free period; M = mean; SD = standard deviation; Italicised = amplitudes (upper panel) and latencies (lower panel); amplitudes = μV; latencies = ms; *d* = effect size Cohen's *d*; 0.2 = small effect, 0.5 = medium effect; 0.8 = large effect.

attentive (MMN) and attentive (P300) condition. RL displayed shorter MMN and P300 latencies for PoA, longer MMN and P300 latencies for voicing, and shorter MMN latencies and longer P300 latencies for MoA compared to the normative group.

After the whole therapy period (τ4), MMN PoA and voicing amplitude did not show any increase or decrease. MMN MoA amplitude increased. P300 PoA, voicing, and MoA amplitude increased, whereas latency for PoA and voicing also increased. Behaviourally, RL evolved from 14.28% correctly identified deviant trials to 100% correctly identified

Table 4. Results bootstrap analysis for ERP amplitudes and latencies—effect of therapy.

	MMN PoA		MMN voicing		MMN MoA		P300 PoA		P300 voicing		P300 MoA		N400 RW		N400 PW	
	T1–T4	T4–T5	T1–T4	T4–T5	T1–T4	T4–T5	T1–T4	T4–T5	T1–T4	T4–T5	T1–T4	T4–T5	T1–T4	T4–T5	T1–T4	T4–T5
FP1						↓*							↑*		↑*	
F7		↓*													↑**	↓**
F3						↓*									↑*	
C3						↓*	↑*		↑*							
T3						↓*										
T5						↓**										
P3						↓*	↑*									
FPz							↑***		↑*	↓*	↑***	↓***			↑*	↓*
Fz							↑*								↑**	↓*
Cz				∨*		↓*	↑*	↓*	↑***	↓*		↓*			↑*	
Pz						↓*	↑*		↑**	↓*					↑*	
FP2						↓*	↑**	↓*				↓*			↑**	↓*
F8		↓*			↑*	↓**	↑*									↓*
F4		↓*			↑*	↓*	↑*	↓*	∧*			↓*			↑*	
C4				∨*		↓*			↑***	↓**					↑*	
T4						↓*			↑*	↓**						
T6					↑*	↓*			↑*	↓*						↓*
P4							*↑∧*		↑**	↓**					↑*	

Notes: T1–T4 = after therapy period; T4–T5 = after therapy-free period; ↑ = amplitude increase; ∨ = latency decrease; ↓ = amplitude decrease; ∧ = latency increase; FP1 = left prefrontal electrode; F7 and F3 = left anterior frontal electrodes; C3 = left posterior frontal electrode; T3 = left anterior temporal electrode; T5 = left posterior temporal electrode; P3 = left parietal electrode; FPz = central prefrontal electrode; Fz = central anterior frontal electrode; Cz = central posterior frontal electrode; Pz = central parietal electrode; FP2 = right prefrontal electrode; F8 and F4 = right anterior frontal electrodes; C4 = right posterior frontal electrode; T4 = right anterior temporal electrode; T6 = right posterior temporal electrode; P4 = right parietal electrode.

* $p = <.05$; ** $p = <.01$; *** $p = <.001$.

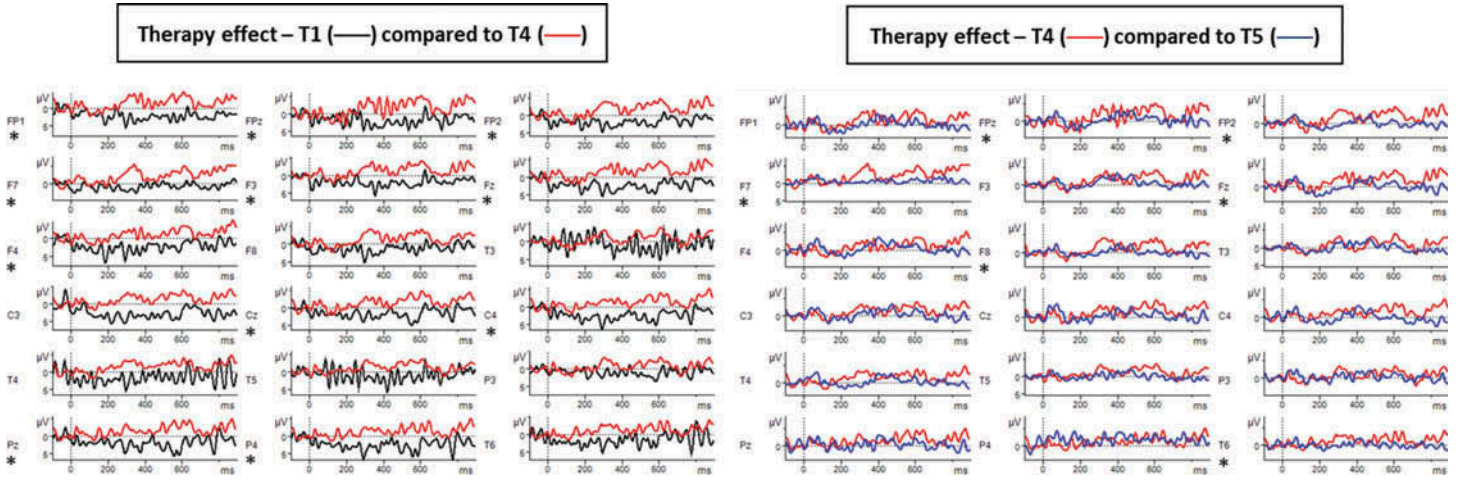

Figure 3. N400 PW before and after the whole therapy period (τ1, τ4) and after the therapy-free period (τ5). [To view this figure in colour, please see the online version of this Journal.]

The N400 in response to PW is represented at every electrode site (except O1 and Oz) before and after therapy and after the therapy-free period. τ1 = initial evaluation moment (*black*); τ4 = evaluation after whole therapy period (*red*); τ5 = evaluation after therapy-free period (*blue*); * significant difference in the Bootstrap analysis.

deviant trials for P300 PoA, from 57.69% to 87.5% correctly identified deviant trials for P300 voicing and from 90.32% to 100% correctly identified deviant trials for P300 MoA.

After the therapy-free period (τ4–τ5), the MMN PoA amplitude decreased, MMN voicing latencies decreased, and there was a general MMN MoA amplitude decrease. P300 PoA, voicing, and MoA amplitude decreased. Behaviourally, RL's response rate remained stable for P300 PoA, increased from 87.5% to 97.43% correctly identified deviant trials for P300 voicing and slightly decreased from 100% to 96.29% correctly identified deviant trials for P300 MoA.

Auditory word recognition

At the initial evaluation moment (τ1), RL showed smaller N400 RW and N400 PW amplitudes than the normative group. Shorter N400 RW latencies and longer N400 PW latencies were found compared to the normative group.

After the whole therapy period (τ1–τ4), N400 RW and PW amplitude increased. No significant differences were identified concerning latency values.

After the therapy-free period (τ5), N400 RW amplitude remained stable, whereas N400 PW amplitudes decreased. No significant differences were identified concerning latency values.

Effect of therapy per period (intensive therapy vs. conventional therapy)

Behavioural results

The largest improvement on the AAT was observed after the first intensive therapy period (τ2). No significant changes could be reported after the conventional therapy period (τ3) and the second intensive therapy period (τ4).

The score on PALPA 1 remained stable after the first intensive therapy block (τ2), reduced moderately ($d = -3.64$) after the conventional therapy period (τ3), and restored again ($d = 4.85$) after the second intensive therapy period (τ4). RL achieved the maximum score on PALPA 2 at every evaluation moment (τ2, τ3, and τ4). Lexical decision of PW (PALPA 5) ($d = 5.52$), repetition of PW (PALPA 8) ($d = 4.62$), and verbal attention (PALPA 12) ($d = 2.87$) showed an improvement after the first intensive therapy period (τ2). No changes in effect sizes were present after the conventional therapy period (τ3) and the second intensive therapy period (τ4). The effect sizes of all PALPA tests are represented in Table 2.

Neurophysiological results

The topographical distribution of the amplitude and latency alterations after the first and second intensive therapy period (τ2; τ4) and after the conventional therapy period (τ3) can be found in Table 5. A clear description of an interpretation of the electrode denomination is provided in the legend. The ERP waveform of the N400 PW before and after the intensive therapy periods (τ2; τ4) and conventional therapy period (τ3) is represented in Figure 4.

Auditory phoneme discrimination

After the first intensive therapy period (τ2), MMN PoA amplitude increased. P300 PoA amplitude decreased, while P300 PoA latency significantly increased. P300 MoA

Table 5. Results of bootstrap analysis for ERP amplitudes and latencies—effect of therapy intensity.

	MMN PoA			MMN voicing			MMN MoA			P300 PoA			P300 voicing			P300 MoA			N400 RW			N400 PW		
	T1–T2	T2–T3	T3–T4	T1–T2	T2–T3	T3–T4	T1–T2	T2–T3	T3–T4	T1–T2	T2–T3	T3–T4	T1–T2	T2–T3	T3–T4	T1–T2	T2–T3	T3–T4	T1–T2	T2–T3	T3–T4	T1–T2	T2–T3	T3–T4
FP1		∧*																				↑*		
F7		∧*						↑**	↓*	↓*				↑*			↑**	↓**				↑**	↓*	↑**
F3	↑*	∧*												↑*			↑*					↑**	↓**	↑**
C3		∧*								↓*	↑**				↓*							↑*	↓*	
T3		∧*						↑*						↑*	↓*								↓*	
T5										↓***				↑*			↑*	↓**						
P3																			↑*			↑**	↓*	
FPz		∧*										↑***		↑*									↓*	↑**
Fz		∧*										↑*										↑*	↓*	↑**
Cz		∧*																				↑*	↓**	↑**
Pz		∧*								∧*	↑*			↑*		↑*						↑*	↓*	↑*
FP2		∧*										↑*					↑**							↑*
F8		∧*						↑*			↑*						↑*							
F4		∧*										↑*		↑*								↑*		↑*
C4		∧*									↑*			↑*								↑*	↓*	↑*
T4																↑*								
T6									∨*							↑*						↑*	↓**	↑*
P4		∧*								*↓∧*	↑*					↑*						↑**	↓**	↑*

Notes: T1–T2 = after first intensive therapy; T2–T3 = after conventional therapy; T3–T4 = after second intensive therapy; ↑ = amplitude increase; ∨ = latency decrease; ↓ = amplitude decrease; ∧ = latency increase;FP1 = left prefrontal electrode; F7 and F3 = left anterior frontal electrodes; C3 = left posterior frontal electrode; T3 = left anterior temporal electrode; T5 = left posterior temporal electrode; P3 = left parietal electrode; FPz = central prefrontal electrode; Fz = central anterior frontal electrode; Cz = central posterior frontal electrode; Pz = central parietal electrode; FP2 = right prefrontal electrode; F8 and F4 = right anterior frontal electrodes; C4 = right posterior frontal electrode; T4 = right anterior temporal electrode; T6 = right posterior temporal electrode; P4 = right parietal electrode. * $p = <.05$; ** $p = <.01$; *** $p = <.001$.

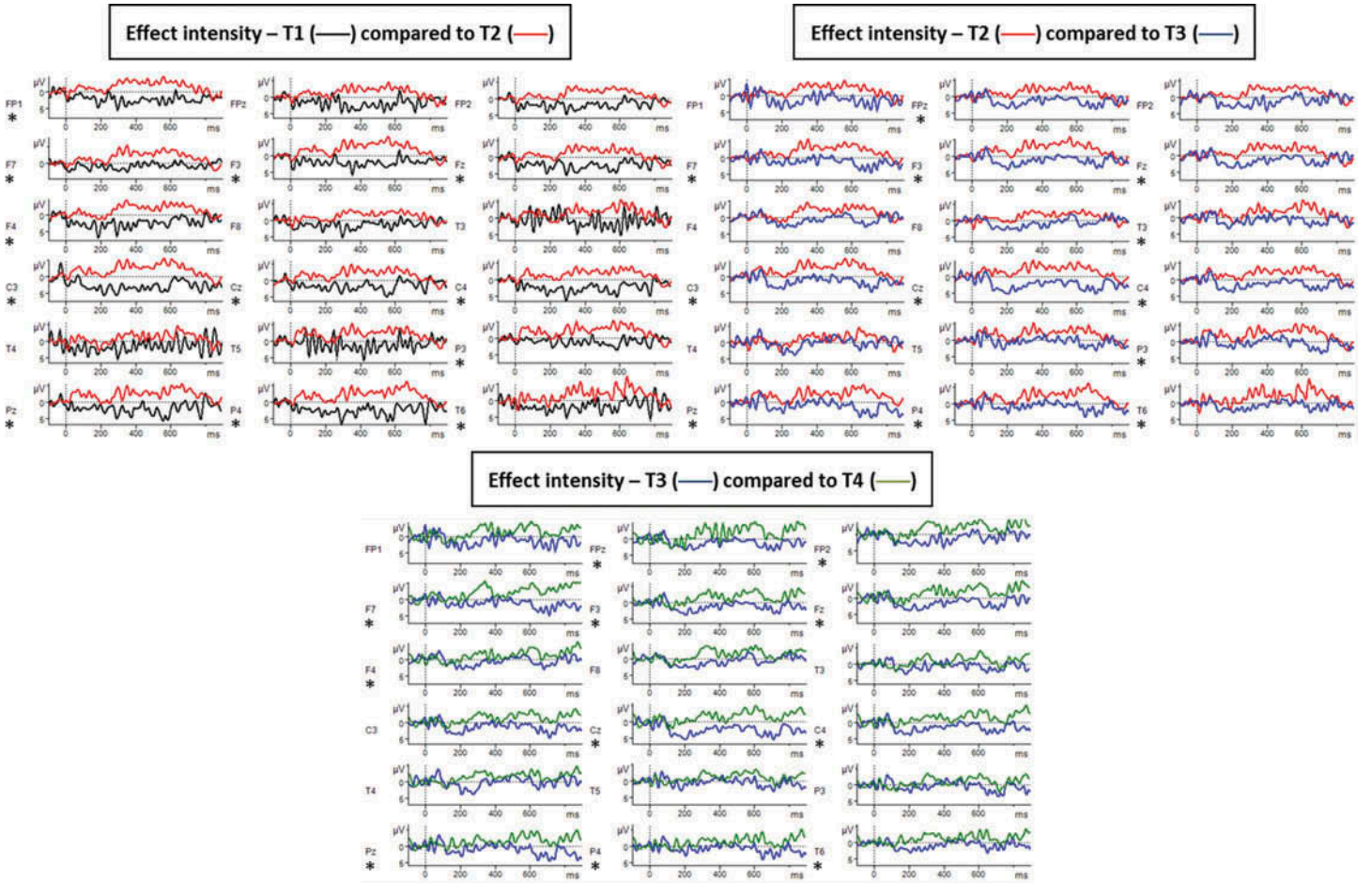

Figure 4. N400 PW before and after the intensive therapy periods (τ2, τ4) and conventional therapy period (τ3). [To view this figure in colour, please see the online version of this Journal.]
The N400 in response to PW is represented at every electrode site (except O1 and Oz) before and after both intensive therapies and before and after conventional therapy. τ1, initial evaluation moment (black); τ2, evaluation after first intensive therapy (red); τ3, evaluation after conventional therapy (blue); τ4, evaluation after second intensive therapy (green); * significant difference in the Bootstrap analysis.

amplitude significantly increased. Behaviourally, RL evolved from 14.28% correctly identified deviant trials to 70.58% correctly identified deviant trials for P300 PoA, from 57.69% to 100% correctly identified deviant trials for P300 voicing, and from 90.32% to 88.57% correctly identified deviant trials for P300 MoA.

After the conventional therapy period (τ3), MMN PoA latency increased. MMN MoA amplitude increased. P300 PoA, voicing, and MoA amplitude increased. Behaviourally, RL evolved from 70.58% correctly identified deviant trials to 97.22% correctly identified deviant trials for P300 PoA, remained stable for P300 voicing, and evolved from 88.57% to 92.59% correctly identified deviant trials for P300 MoA.

After the second intensive therapy period (τ4), MMN MoA amplitude decreased, whereas its latency decreased as well. P300 PoA amplitude increased, whereas P300 voicing and MoA amplitude decreased. Behaviourally, RL's response rate remained stable for P300 PoA, decreased from 100% to 87.5% correctly identified deviant trials for P300 voicing, and increased from 92.59% to 100% correctly identified deviant trials for P300 MoA.

Auditory word recognition

After the first intensive therapy period (τ2), N400 RW and PW amplitude increased. No significant differences were identified concerning latency values.

After the conventional therapy period (τ3), N400 PW amplitude decreased. No significant differences were identified concerning N400 PW latency and N400 RW amplitude and latency.

After the second intensive therapy period (τ4), N400 PW amplitude increased again. No significant differences were identified concerning N400 PW latency and N400 RW amplitude and latency.

Discussion

The aim of the present study was to objectify the effect of language therapy during the acute and post-acute phase after stroke and to compare the language results achieved during the whole therapy period with the language abilities after a period without any form of language therapy. By further subdividing the whole therapy period into different therapy blocks, the present study sought to gain additional insight into possible therapy-related influencing variables.

Overall therapy effect

After the whole therapy period, RL showed a substantial improvement on all behavioural measures, except for verbal attention (PALPA 12). The neurophysiological measures confirmed the behavioural findings, as the P300, MMN (only for MoA), and N400 ERP components were aberrant before therapy when compared to normative data and improved after therapy. Throughout the therapy-free period, the behavioural improvement was maintained and the spontaneous language production of the AAT reached a maximum score. In contrast to the behavioural results, neurophysiological correlates showed a decline after the therapy-free period. Based on these findings, RL seemed to benefit from therapeutic intervention in the early phase after stroke, although the long-term effect is mixed due to the discrepancy between the behavioural and neurophysiological results. Continued follow-up would be necessary to identify further neurophysiological evolution

and to get a better understanding of its relation to the behavioural outcome. It must be mentioned though that the major behavioural improvement of RL, especially on the AAT, was already established after the first intensive therapy period (τ2), which is ±4 weeks after stroke. The time after stroke and the large improvement of RL's language performance most likely implies that spontaneous recovery contributed to RL's improved language abilities. However, up to now it is still not possible to disentangle with certainty the effects of language therapy from the effects of spontaneous recovery in the acute stage of stroke (Pulvermüller & Berthier, 2008). Although a growing number of studies indicate the efficacy of aphasia therapy early after stroke (Brady et al., 2012; Godecke et al., 2012; Mattioli et al., 2014), two studies have recently postulated that language intervention early after stroke, in the acute and post-acute stage of aphasia, may not be beneficial (Bowen et al., 2012) or even not recommended (Laska et al., 2011). A possible explanation for the lack of therapy success in these studies might be the low intensity (maximum of 3 hr and 45 min per week) and the use of functional outcome measures rather than impairment-specific measures. Moreover, Bowen et al. (2012) did not differentiate between patients with dysarthria and patients with aphasia when interpreting the effect of language therapy, which might be considered as a methodological weakness. The studies conducted by Bowen et al. (2012) and Laska et al. (2011) both employed a randomised controlled trial (RCT) design. Such design can lead to contradictory conclusions regarding the usefulness of aphasia therapy, considering the complex heterogeneity of a group of patients with aphasia. This makes RCTs a criticised study design in aphasia research and therefore there has been a plea to encourage sufficiently detailed single-case patient studies and carry out meta-analyses instead of using RCTs (Code, 2000; Robey et al., 1999). By focusing on a single patient with aphasia, the present study contributed to a valuable collection of single-case studies investigating the effects of aphasia therapy early after stroke.

The implementation of neurophysiological measures in the present study made it possible to refine the diagnostic and therapeutic monitoring with respect to neuronal modulation. Changes in language performance were detected with neurophysiological tasks when no behavioural alterations were measurable. For example, neurophysiological correlates showed a decline after the therapy-free period, in contrast to the behavioural results that maintained at a level close to ceiling and even showed a progression of spontaneous language production. The neurophysiological examination also obviated the problem of ceiling effects. Some behavioural measures (PALPA 1, 2, 5 RW) already reached the maximum scores at the initial evaluation moment (τ1), whereas at that point the P300, MMN, and N400 ERP components were aberrant when compared to normative data. These more refined results on the neurophysiological measures are in line with a previous study where patients with aphasia performed seemingly normal on behavioural language tasks despite the fact that their ERPs still revealed subtle deficiencies in central auditory processing (Becker & Reinvang, 2007). The neurophysiological measures also provided information about the effects on the neuronal localisation of phonological input processes. After the therapy period, the increased MMN MoA responses occurred in right-lateralised frontotemporal areas and the N400 PW amplitude increased significantly in bilateral anterior frontal areas and in right posterior frontoparietal areas. According to the recovery model posed by Saur et al. (2006), in the first weeks and months after stroke, an upregulation of homologue right hemisphere language areas can coincide with a significant improvement of language performance. So, it seems that a contribution of right hemispheric areas at this point after stroke (τ4) was not counterproductive for RL. Moreover, the increased P300 responses in bilateral frontoparietal areas demonstrate an upregulation of lesional and perilesional areas in the left hemisphere. A re-shift to the left

hemisphere might be related to a favourable neuronal reorganisation and further beneficial recovery (Fridriksson et al., 2012). Thus, at τ4 RL demonstrates a combination of recovery patterns. At 1 year post–stroke, one can expect a higher participation of the left hemisphere (Saur & Hartwigsen, 2012; Saur et al., 2006). However, in contrast to this, more left-lateralised ERPs could not be established for RL at approximately 10 months post-onset of the stroke. Moreover, there was even a significant amplitude decrease in left frontal areas for the MMN (PoA and MoA) and N400 PW. These ERP results indicate that RL's neurophysiological gains were not maintained after the therapy-free period. It is possible that with an increased dosage or duration of behavioural intervention a progression towards a more normal activation pattern would be achieved (Kleim & Jones, 2008; van Hees et al., 2014). Perhaps when a re-shift towards the left hemisphere was already visible directly after the whole therapy period, the neuronal networks would have been strong enough to prevent a decrease. On the other hand, these neurophysiological alterations might reflect a change towards a more effective, yet modified pattern of neural activation supporting successful phonological input processing after language therapy (Laganaro, Morand, Schwitter, Zimmermann, & Schnider, 2008; Wilson et al., 2012). The implementation of neurophysiological measures made it possible to identify plasticity effects in terms of neuronal localisation and modulation, which would not be possible when only the behavioural measures were considered. The combination of findings of the present case study and those of previous studies using ERPs in the monitoring of aphasia therapy encourages the implementation of ERPs in therapeutic follow-up of patients with aphasia (Breier, Maher, Schmadeke, Hasan, & Papanicolaou, 2007; Pulvermüller et al., 2005; Wilson et al., 2012).

Effect of therapy per period

Disentangling the intensive and conventional therapy within the present study reveals some form of dichotomy within the whole therapy period, as demonstrated by differences in the neurophysiological and behavioural outcome measures. The behavioural results revealed a decline in auditory discrimination for PW (PALPA 1) after the conventional therapy, which restored again after the second intensive therapy period. However, for the other behavioural measures (PALPA 2, PALPA 5 RW, PALPA 8, and almost all subtests of the AAT), no changes could be reported after the conventional and second intensive therapy period, most likely due to the fact that RL already reach ceiling scores after the first intensive therapy period (τ2). The most striking neurophysiological difference between the intensive therapy periods and conventional therapy period were the N400 alterations, especially the N400 in response to PW. After each intensive therapy period, N400 PW amplitude increased, whereas after the conventional therapy the N400 PW amplitude decreased. The neurophysiological results reflect the results on the behavioural tests comprising PW (PALPA 1, 5 PW, and 8), which improve after the intensive therapy periods and show a decline or a maintenance at ceiling level after the conventional therapy period. Taken together with the ceiling effect being obviated by the N400 PW amplitude, it becomes clear that this neurophysiological correlate is sensitive enough to measure therapy effects. Moreover, the N400 PW amplitude can be seen as a pure language measure, targeting sublexical representations that are essential for learning and processing new, unfamiliar, or ambiguous words (Vitevitch, 2003). So, the intensive therapy periods seem to improve RL's capacity to address his sublexical capacities, which is important for fluent auditory language processing. With respect to the N400 RW amplitude, the same pattern as for the N400 PW amplitude is noticeable, but only after the first intensive

therapy period. The N400 amplitude increase in response to RW and PW contrasts with another study applying the N400 potential to measure aphasia therapy effects, which demonstrated no differences in amplitudes pre- and post-therapy (Wilson et al., 2012). In the Wilson et al. (2012) study, the clinical language improvement of the patients with aphasia was associated with a shift from a more right-lateralised distribution to a more left-lateralised N400. In contrast, Pulvermüller et al. (2005) found that intensive therapy can lead to an amplitude increase between 250 and 300 ms in response to meaningful words. Together with the present study, these ERP changes suggest that intensive therapy can induce significant neurophysiological modifications. However, the neurophysiological correlates of auditory discrimination (MMN and P300) fluctuated throughout the intensive and conventional therapy blocks, yet a positive trend emerges when considering a longer timeframe. Thus, MMN and P300 seem worth including in a neurophysiological therapy-oriented evaluation (Ilvonen et al., 2003; Nolfe et al., 2006).

However, when investigating therapeutic effects within the first three months after stroke, spontaneous neuronal recovery is an important confounding factor (Lazar, Speizer, Festa, Krakauer, & Marshall, 2008). The major part of recovery is expected to occur within the first three months after stroke (El Hachioui, van de Sandt-Koenderman, Dippel, Koudstaal, & Visch-Brink, 2011; Lendrem & Lincoln, 1985), but it is difficult to determine with certainty whether neurophysiological or behavioural changes observed in acute patients are due to pure neuronal reorganisation or a by-product of a spontaneous restitution processes (Pulvermüller & Berthier, 2008). However, it seems that aphasia therapy in the acute stage of stroke has shown benefits over or can enhance spontaneous recovery (Godecke et al., 2012; Lazar et al., 2010), whereby intensity seems to play a critical role (Godecke et al., 2014). Furthermore, the decline of auditory discrimination after the conventional therapy period, which was still within the first three months after stroke, does not seem to correspond to what one would expect of successful spontaneous recovery. The behavioural deterioration of auditory discrimination together with the lack of further improvement of the amplitude of the N400 PW after the conventional therapy favours at least a partial contribution of intensive treatment during the first intensive therapy period.

Based on the aforementioned results, it can be suggested that RL benefited, besides his spontaneous recovery, from intensive language treatment, as it yielded an improvement in his language performance compared to the deterioration of the auditory discrimination of PW after the conventional therapy. Although all therapy periods consisted of impairment-based assignments, the specific content of all three therapy periods varied. The first intensive therapy period focussed on the mapping of phonological information onto semantic representations, while during the second intensive therapy sublexical processes were more emphasised. It was a conscious decision to adapt therapy content to RL's needs, based on the most recent diagnostic information available and according to clinical best practice. Notwithstanding, the variation in content might have affected the behavioural test results (Doesborgh et al., 2004) or neuronal mechanisms (van Hees et al., 2014), it cannot provide a sufficient answer why both intensive therapy periods yield the same positive change of N400 PW amplitude in similar brain regions, which targets sublexical processes, while the content of the first intensive therapy did not focus on sublexical processes. Taken together with the fact that the intensity (duration and frequency) of both intensive therapy periods were equal and different from the conventional therapy period, it is most likely that the intensity influenced RL's therapeutic outcome (alterations of the behavioural PALPA 1 and neurophysiological N400 PW amplitude). Although a large number of studies provide evidence for the efficacy of intensive

treatment (e.g., Breitenstein et al., 2009; Meinzer, Rodriguez, & Gonzalez Rothi, 2012; Godecke et al., 2013; Pulvermüller et al., 2005), other studies claim that intensity does not provide an added value to therapy results (Bakheit et al., 2007; Cherney, Patterson, & Raymer, 2011; Hinckley & Carr, 2005). However, when taking a closer look at the methodology, there seems to be a difference compared to the present study concerning the actual definition of intensity and type of therapy. For example, the present study introduced 10 hr per week as the intensive treatment, based on the results of Bhogal et al. (2003), which suggest that an average of 8.8 hr per week is necessary to achieve positive effects. Bakheit et al. (2007) introduced an intensive treatment of only 5 hr per week, so it is possible that this was not intensive enough to elicit potential therapy effects. In contrast with the present study, which focused on an impairment-based approach, Hinckley and Carr (2005) provided a communicative-based therapy programme. Taken together with the findings of Godecke et al. (2014), RL's behavioural and neurophysiological language improvement seems to be based on the combination of three essential therapeutic elements, intensifying spontaneous recovery, namely intensive, impairment-based treatment in the (post) acute stage.

Finally, the present single-case study carries some methodological limitations. First, there were no tests administered assessing functional communication abilities or quality of life. Perhaps this would provide more information in light of the ceiling effects of the PALPA and AAT results, considering that the SLPs noticed the presence of subtle language difficulties during spontaneous speech. Second, for an optimal single-case study, multiple evaluation moments should be embedded during one intervention period to allow proper statistical comparisons between intervention periods (Waddell, Nassar, Gustafson, 2011). For the present study, this was not the case. However, this would mean that the PALPA tasks, the AAT, and the EEG recording would have to take place weekly, which would be quite burdensome for the patient, considering the already intensive therapy periods.

Conclusion

The implementation of ERPs provided added value during this single-case therapy follow-up. Ceiling effects at the behavioural level could be obviated and underlying, advantageous or disadvantageous, neuronal activation patterns of certain behavioural improvements could be identified. The alterations of the N400 in particular proved to be very sensitive for mapping the effects of intensity on therapy progression. RL benefited from early therapeutic intervention after stroke, as was shown by a general language improvement, marked by behavioural and neurophysiological indicators 4 months after stroke. The deterioration of certain neurophysiological and behavioural measures after the conventional therapy might suggest that therapy intensity was an influencing variable throughout the therapy periods. Moreover, the behavioural and neurophysiological evolution throughout the different therapy periods provides additional support that RL's early language improvement within the first four months after stroke most likely intensifies, at least in part, spontaneous recovery mechanisms.

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References

Aerts, A., Santens, P., & De Letter, M. (2012). *Flemish normative data of the first column PALPA 1 and PALPA 2*. Unpublished manuscript.

Aerts, A., Van Mierlo, P., Hartsuiker, R. J., Hallez, H., Santens, P., & De Letter, M. (2013). Neurophysiological investigation of phonological input: Aging effects and development of normative data. *Brain and Language*, *125*, 253–263. doi:10.1016/j.bandl.2013.02.010

Allen, L., Mehta, S., McClure, J. A., & Teasell, R. (2012). Therapeutic interventions for aphasia initiated more than six months post stroke: A review of the evidence. *Topics in Stroke Rehabilitation*, *19*, 523–535. doi:10.1310/tsr1906-523

Bakheit, A. M. O., Shaw, S., Barrett, L., Wood, J., Carrington, S., Griffiths, S., … Koutsi, F. (2007). A prospective, randomized, parallel group, controlled study of the effect of intensity of speech and language therapy on early recovery from poststroke aphasia. *Clinical Rehabilitation*, *21*, 885–894. doi:10.1177/0269215507078486

Bastiaanse, R., Bosje, M., & Visch-Brink, E. (1995). *Psycholinguistic assessment of language processing in aphasia: The Dutch version*. Hove: Lawrence Erlbaum Associates.

Bastiaanse, R., Edwards, S., & Rispens, J. (2002). *The verb and sentence test (VAST)*. Thurston, Suffolk: Thames Valley Test Company.

Becker, F., & Reinvang, I. (2007). Successful syllable detection in aphasia despite processing impairments as revealed by event-related potentials. *Behavioral and Brain Functions*, *3*, 6. doi:10.1186/1744-9081-3-6

Belin, P., Van Eeckhout, P., Zilbovicius, M., Remy, P., Francois, C., Guillaume, S., … Samson, Y. (1996). Recovery from nonfluent aphasia after melodic intonation therapy: A PET study. *Neurology*, *47*, 1504–1511. doi:10.1212/WNL.47.6.1504

Bhogal, S. K., Teasell, R., & Speechley, M. (2003). Intensity of aphasia therapy, impact on recovery. *Stroke*, *34*, 987–993. doi:10.1161/01.str.0000062343.64383.d0

Bowen, A., Hesketh, A., Patchick, E., Young, A., Davies, L., Vail, A., … Tyrrell, P. (2012). Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria: A randomised controlled trial. *British Medical Journal*, *345*, e4407. doi:10.1136/bmj.e4407

Brady, M. C., Kelly, H., Godwin, J., & Enderby, P. (2012). Speech and language therapy for aphasia following stroke. *Cochrane Database of Systematic Reviews*, *5*, 234. doi:10.1002/14651858.CD000425.pub3

Breier, J. I., Castillo, E. M., Boake, C., Billingsley, R., Maher, L., Francisco, G., & Papanicolaou, A. C. (2004). Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. *Neuroimage*, *23*, 1308–1316. doi:10.1016/j.neuroimage.2004.07.069

Breier, J. I., Maher, L. M., Schmadeke, S., Hasan, K. M., & Papanicolaou, A. C. (2007). Changes in language-specific brain activation after therapy for aphasia using magnetoencephalography: A case study. *Neurocase*, *13*, 169–177. doi:10.1080/13554790701448200

Breitenstein, P. D. C., Kramer, K., Meinzer, M., Baumgärtner, A., Flöel, A., & Knecht, S. (2009). Intensives Sprachtraining bei Aphasie. *Der Nervenarzt*, *80*, 149–154. doi:10.1007/s00115-008-2571-6

Cherney, L. R., Patterson, J. P., & Raymer, A. M. (2011). Intensity of aphasia therapy: Evidence and efficacy. *Current Neurology and Neuroscience Reports*, *11*, 560–569. doi:10.1007/s11910-011-0227-6

Cherney, L. R., Patterson, J. P., Raymer, A., Frymark, T., & Schooling, T. (2008). Evidence-based systematic review: Effects of intensity of treatment and constraint-induced language therapy for individuals with stroke-induced aphasia. *Journal of Speech, Language, and Hearing Research*, *51*, 1282–1299. doi:10.1044/1092-4388(2008/07-0206)

Code, C. (2000). The problem with RCTs. *RCSLT Bulletin*, *574*, 14–15.

Code, C., Torney, A., Gildea-Howardine, E., & Willmes, K. (2010). Outcome of a one-month therapy intensive for chronic aphasia: Variable individual responses. *Seminars in Speech and Language*, *31*, 21–33. doi:10.1055/s-0029-1244950

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. New York, NY: Routledge.
Corsten, S., Mende, M., Cholewa, J., & Huber, W. (2007). Treatment of input and output phonology in aphasia: A single case study. *Aphasiology*, *21*, 587–603. doi:10.1080/02687030701192034
Csépe, V., Osman-Sági, J., Molnár, M., & Gósy, M. (2001). Impaired speech perception in aphasic patients: Event-related potential and neuropsychological assessment. *Neuropsychologia*, *39*, 1194–1208. doi:10.1016/S0028-3932(01)00052-5
Davis, C. H., & Harrington, G. (2006). Intensive semantic intervention in fluent aphasia: A pilot study with fMRI. *Aphasiology*, *20*, 59–83. doi:10.1080/02687030500331841
de Jong-Hagelstein, M., van de Sandt-Koenderman, W. M. E., Prins, N. D., Dippel, D. W. J., Koudstaal, P. J., & Visch-Brink, E. G. (2011). Efficacy of early cognitive-linguistic treatment and communicative treatment in aphasia after stroke: A randomised controlled trial (RATS-2). *Journal of Neurology Neurosurgery and Psychiatry*, *82*, 399–404. doi:10.1136/jnnp.2010.210559
Dickey, L., Kagan, A., Lindsay, M. P., Fang, J. M., Rowland, A., & Black, S. (2010). Incidence and profile of inpatient stroke-induced aphasia in Ontario, Canada. *Archives of Physical Medicine and Rehabilitation*, *91*, 196–202. doi:10.1016/j.apmr.2009.09.020
Doesborgh, S. J. C., van de Sandt-Koenderman, M. W. E., Dippel, D. W. J., Van Harskamp, F., Koudstaal, P. J., & Visch-Brink, E. G. (2004). Effects of semantic treatment on verbal communication and linguistic processing in aphasia after stroke: A randomized controlled trial. *Stroke*, *35*, 141–146. doi:10.1161/01.str.0000105460.52928.a6
El Hachioui, H., van de Sandt-Koenderman, M. W. M. E., Dippel, D. W. J., Koudstaal, P. J., & Visch-Brink, E. G. (2011). A 3-year evolution of linguistic disorders in aphasia after stroke. *International Journal of Rehabilitation Research*, *34*, 215–221. doi:10.1097/MRR.0b013e3283460e65
Ferreira-Santos, F., Silveira, C., Almeida, P. R., Palha, A., Barbosa, F., & Marques-Teixeira, J. (2012). The auditory P200 is both increased and reduced in schizophrenia? A meta-analytic dissociation of the effect for standard and target stimuli in the oddball task. *Clinical Neurophysiology*, *123*, 1300–1308. doi:10.1016/j.clinph.2011.11.036
Fridriksson, J., Richardson, J. D., Fillmore, P., & Cai, B. (2012). Left hemisphere plasticity and aphasia recovery. *Neuroimage*, *60*, 854–863. doi:10.1016/j.neuroimage.2011.12.057
Ghyselinck, M., Custers, R., & Brysbaert, M. (2003). Age-of-acquisition ratings for 2332 Dutch words from 49 different semantic categories. *Psychologica Belgica*, *43*, 181–214.
Godecke, E., Ciccone, N. A., Granger, A. S., Rai, T., West, D., Cream, A., … Hankey, G. J. (2014). A comparison of aphasia therapy outcomes before and after a Very Early Rehabilitation programme following stroke. *International Journal of Language & Communication Disorders*, *49*, 149–161. doi:10.1111/1460-6984.12074
Godecke, E., Hird, K., Lalor, E. E., Rai, T., & Phillips, M. R. (2012). Very early poststroke aphasia therapy: A pilot randomized controlled efficacy trial. *International Journal of Stroke*, *7*, 635–644. doi:10.1111/j.1747-4949.2011.00631.x
Godecke, E., Rai, T., Ciccone, N., Armstrong, E., Granger, A., & Hankey, G. J. (2013). Amount of therapy matters in very early aphasia rehabilitation after stroke: A Clinical prognostic model. *Seminars in Speech and Language*, *34*, 129–141. doi:10.1055/s-0033-1358369
Goral, M., & Kempler, D. (2009). Training verb production in communicative context: Evidence from a person with chronic non-fluent aphasia. *Aphasiology*, *23*, 1383–1397. doi:10.1080/02687030802235203
Graetz, P., De Bleser, R., & Willems, K. (2005). *Akense afasie test*. Amsterdam: Harcourt Test.
Hinckley, J. J., & Carr, T. H. (2005). Comparing the outcomes of intensive and non-intensive context-based aphasia treatment. *Aphasiology*, *19*, 965–974. doi:10.1080/02687030544000173
Ilvonen, T.-M., Kujala, T., Kiesilainen, A., Salonen, O., Kozou, H., Pekkonen, E., … Naatanen, R. (2003). Auditory Discrimination after left-hemisphere stroke: A mismatch negativity follow-up study. *Stroke*, *34*, 1746–1751. doi:10.1161/01.STR.0000078836.26328.3B
Kauhanen, M.-L., Korpelainen, J. T., Hiltunen, P., Määttä, R., Mononen, H., Brusin, E., … Myllyla, V. V. (2000). Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovascular Diseases*, *10*, 455–461. doi:10.1159/000016107
Kawohl, W., Bunse, S., Willmes, K., Hoffrogge, A., Buchner, H., & Huber, W. (2010). Semantic event-related potential components reflect severity of comprehension deficits in aphasia. *Neurorehabilitation and Neural Repair*, *24*, 282–289. doi:10.1177/1545968309348311

Kendall, D. L., Nadeau, S. E., Conway, T., Fuller, R. H., Riestra, A., & Rothi, L. J. G. (2006). Treatability of different components of aphasia - Insights from a case study. *The Journal of Rehabilitation Research and Development*, *43*, 323–335. doi:10.1682/jrrd.2005.01.0014

Keuleers, E., Brysbaert, M., & New, B. (2010). SUBTLEX-NL: A new measure for Dutch word frequency based on film subtitles. *Behavior Research Methods*, *42*, 643–650. doi:10.3758/BRM.42.3.643

Kim, M., & Tomaino, C. M. (2008). Protocol evaluation for effective music therapy for persons with nonfluent aphasia. *Topics in Stroke Rehabilitation*, *15*, 555–569. doi:10.1310/tsr1506-555

Kirmess, M., & Maher, L. M. (2010). Constraint induced language therapy in early aphasia rehabilitation. *Aphasiology*, *24*, 725–736. doi:10.1080/02687030903437682

Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing Research*, *51*, S225–S239. doi:10.1044/1092-4388(2008/018)

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science*, *207*, 203–205. doi:10.1126/science.7350657

Kwon, M. S., Huotilainen, M., Shestakova, A., Kujala, T., Naatanen, R., & Hamalainen, H. (2010). No effects of mobile phone use on cortical auditory change-detection in children: An ERP study. *Bioelectromagnetics*, *31*, 191–199. doi:10.1002/bem.20546

Laganaro, M., Morand, S., Schwitter, V., Zimmermann, C., & Schnider, A. (2008). Normalisation and increase of abnormal ERP patterns accompany recovery from aphasia in the post-acute stage. *Neuropsychologia*, *46*, 2265–2273. doi:10.1016/j.neuropsychologia.2008.02.013

Laska, A. C., Kahan, T., Hellblom, A., Murray, V., & von Arbin, M. (2011). A randomized controlled trial on very early speech and language therapy in acute stroke patients with aphasia. *Cerebrovascular Diseases Extra*, *1*, 66–74. doi:10.1159/000329835

Lazar, R. M., Minzer, B., Antoniello, D., Festa, J. R., Krakauer, J. W., & Marshall, R. S. (2010). Improvement in aphasia scores after stroke is well predicted by initial severity. *Stroke*, *41*, 1485–1488. doi:10.1161/STROKEAHA.109.577338

Lazar, R. M., Speizer, A. E., Festa, J. R., Krakauer, J. W., & Marshall, R. S. (2008). Variability in language recovery after first-time stroke. *Journal of Neurology Neurosurgery and Psychiatry*, *79*, 530–534. doi:10.1136/jnnp.2007.122457

Léger, A., Démonet, J.-F., Ruff, S., Aithamon, B., Touyeras, B., Puel, M., … Cardebat, D. (2002). Neural substrates of spoken language rehabilitation in an aphasic patient: An fMRI study. *Neuroimage*, *17*, 174–183. doi:10.1006/nimg.2002.1238

Lendrem, W., & Lincoln, N. B. (1985). Spontaneous-recovery of language in patients with aphasia between 4 and 34 weeks after stroke. *Journal of Neurology Neurosurgery and Psychiatry*, *48*, 743–748. doi:10.1136/jnnp.48.8.743

Lin, Y., Wu, W., Wu, C., Liu, B., & Gao, X. (2013). Extraction of mismatch negativity using a resampling-based spatial filtering method. *Journal of Neural Engineering*, *10*. doi:10.1088/1741-2560/10/2/026015

Marsi, E., Busser, B., Daelemans, W., Hoste, V., & Reynaert, M. (2002). Combining information sources for memory-based pitch accent placement. In *International conference on spoken language processing* (pp. 1273–1276). Denver, CO: ISCA.

Mattioli, F., Ambrosi, C., Mascaro, L., Scarpazza, C., Pasquali, P., Frugoni, M., … Gasparotti, R. (2014). Early aphasia rehabilitation is associated with functional reactivation of the left inferior frontal gyrus: A pilot study. *Stroke*, *45*, 545–552. doi:10.1161/STROKEAHA.113.003192

Meinzer, M., Djundja, D., Barthel, G., Elbert, T., & Rockstroh, B. (2005). Long-term stability of improved language functions in chronic aphasia after constraint-induced aphasia therapy. *Stroke*, *36*, 1462–1466. doi:10.1161/01.STR.0000169941.29831.2a

Meinzer, M., Elbert, T., Wienbruch, C., Djundja, D., Barthel, G., & Rockstroh, B. (2004). Intensive language training enhances brain plasticity in chronic aphasia. *BMC Biology*, *2*, 20. doi:10.1186/1741-7007-2-20

Meinzer, M., Rodriguez, A. D., & Gonzalez Rothi, L. J. (2012). First decade of research on constrained-induced treatment approaches for aphasia rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *93*(S1), S35–S45. doi:10.1016/j.apmr.2011.06.040

Meinzer, M., Streiftau, S., & Rockstroh, B. (2007). Intensive language training in the rehabilitation of chronic aphasia: Efficient training by laypersons. *Journal of the International Neuropsychological Society*, *13*, 846–853. doi:10.1017/s1355617707071111

Näätänen, R., Gaillard, A. W. K., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychologica*, *42*, 313–329. doi:10.1016/0001-6918(78)90006-9

Nolfe, G., Cobianchi, A., Mossuto-Agatiello, L., & Giaquinto, S. (2006). The role of P300 in the recovery of post-stroke global aphasia. *European Journal of Neurology*, *13*, 377–384. doi:10.1111/j.1468-1331.2006.01237.x

Oruç, I., Krigolson, O., Dalrymple, K., Nagamatsu, L. S., Handy, T. C., & Barton, J. J. S. (2011). Bootstrap analysis of the single subject with event related potentials. *Cognitive Neuropsychology*, *28*, 322–337. doi:10.1080/02643294.2011.648176

Parker, R. I. (2006). Increased reliability for single-case research results: Is the bootstrap the answer? *Behavior Therapy*, *37*, 326–338. doi:10.1016/j.beth.2006.01.007

Persad, C., Wozniak, L., & Kostopoulos, E. (2013). Retrospective analysis of outcomes from two intensive comprehensive aphasia programs. *Topics in Stroke Rehabilitation*, *20*, 388–397. doi:10.1310/tsr2005-388

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., … Taylor, M. J. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology*, *37*, 127–152. doi:10.1111/1469-8986.3720127

Pulvermüller, F., & Berthier, M. L. (2008). Aphasia therapy on a neuroscience basis. *Aphasiology*, *22*, 563–599. doi:10.1080/02687030701612213

Pulvermüller, F., Hauk, O., Zohsel, K., Neininger, B., & Mohr, B. (2005). Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. *Neuroimage*, *28*, 481–489. doi:10.1016/j.neuroimage.2005.06.038

Pulvermuller, F., Mohr, B., & Lutzenberger, W. (2004). Neurophysiological correlates of word and pseudo-word processing in well-recovered aphasics and patients with right-hemispheric stroke. *Psychophysiology*, *41*, 584–591. doi:10.1111/j.1469-8986.2004.00188.x

Pulvermuller, F., Neininger, B., Elbert, T., Mohr, B., Rockstroh, B., Koebbel, P., & Taub, E. (2001). Constraint-induced therapy of chronic aphasia after stroke. *Stroke*, *32*, 1621–1626. doi:10.1161/01.STR.32.7.1621

Robey, R. R. (1998). A meta-analysis of clinical outcomes in the treatment of aphasia. *Journal of Speech Language and Hearing Research*, *41*, 172–187. doi:10.1044/jslhr.4101.172

Robey, R. R., Schultz, M. C., Crawford, A. B., & Sinner, C. A. (1999). Review: Single-subject clinical-outcome research: Designs, data, effect sizes, and analyses. *Aphasiology*, *13*, 445–473. doi:10.1080/026870399402028

Rochon, E., Leonard, C., Burianova, H., Laird, L., Soros, P., Graham, S., & Grady, C. (2010). Neural changes after phonological treatment for anomia: An fMRI study. *Brain and Language*, *114*, 164–179. doi:10.1016/j.bandl.2010.05.005

Rodriguez, A. D., Worrall, L., Brown, K., Grohn, B., McKinnon, E., Pearson, C., … Copland, D. A. (2013). Aphasia LIFT: Exploratory investigation of an intensive comprehensive aphasia programme. *Aphasiology*, *27*, 1339–1361. doi:10.1080/02687038.2013.825759

Rose, M. L., Cherney, L. R., & Worrall, L. E. (2013). Intensive comprehensive aphasia programs: An international survey of practice. *Topics in Stroke Rehabilitation*, *20*, 379–387. doi:10.1310/tsr2005-379

Rousselet, G. A., Husk, J. S., Pernet, C. R., Gaspar, C. M., Bennett, P. J., & Sekuler, A. B. (2009). Age-related delay in information accrual for faces: Evidence from a parametric, single-trial EEG approach. *Bmc Neuroscience*, *10*. doi:10.1186/1471-2202-10-114

Saur, D., & Hartwigsen, G. (2012). Neurobiology of language recovery after stroke: Lessons from neuroimaging studies. *Archives of Physical Medicine and Rehabilitation*, *93*, S15–S25. doi:10.1016/j.apmr.2011.03.036

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain*, *129*, 1371–1384. doi:10.1093/brain/awl090

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science*, *150*, 1187–1188. doi:10.1126/science.150.3700.1187

Szaflarski, J. P., Ball, A., Grether, S., Al-Fwaress, F., Griffith, N. M., Neils-Strunjas, J., & Reichhardt, R. (2008). Constraint-induced aphasia therapy stimulates language recovery in patients with chronic aphasia after ischemic stroke. *Medical Science Monitor*, *14*, CR243–250.

Tyler, L. K., Wright, P., Randall, B., Marslen-Wilson, W. D., & Stamatakis, E. A. (2010). Reorganization of syntactic processing following left-hemisphere brain damage: Does right-hemisphere activity preserve function? *Brain*, *133*, 3396–3408. doi:10.1093/brain/awq262

van Hees, S., McMahon, K., Angwin, A., de Zubicaray, G., & Copland, D. A. (2014). Neural activity associated with semantic versus phonological anomia treatments in aphasia. *Brain and Language*, *129*, 47–57. doi:10.1016/j.bandl.2013.12.004

Van Strien, J. W. (1992). Classificatie van left- en rechtshandige proefpersonen. *Nederlands Tijdschrift Voor De Psychologie*, *47*, 88–92

Visch-Brink, E. G., & Denes, G. (1993). A European base-line test for word-picture processing. In P. J. Stachowiak, R. de Bleser, G. Deloche, R. Kaschell, H. Kremin, P. North, ... B. Wilson (Eds.), *Developments in the assessment and rehabilitation of brain-damaged patients* (pp. 211–216). Tübingen: Gunter Narr Verlag.

Vitevitch, M. S. (2003). The influence of sublexical and lexical representations on the processing of spoken words in English. *Clinical Linguistics & Phonetics*, *17*, 487–499. doi:10.1080/0269920031000107541

Waddell, D. E., Nassar, S. L., & Gustafson, S. A. (2011). Single-case design in psychophysiological research: Part II: Statistical analytic approaches. *Journal of Neurotherapy*, *15*, 160–169. doi:10.1080/10874208.2011.570693

Wilson, K. R., O'Rourke, H., Wozniak, L. A., Kostopoulos, E., Marchand, Y., & Newman, A. J. (2012). Changes in N400 topography following intensive speech language therapy for individuals with aphasia. *Brain and Language*, *123*, 94–103. doi:10.1016/j.bandl.2012.06.005

Winans-Mitrik, R. L., Hula, W. D., Dickey, M. W., Schumacher, J. G., Swoyer, B., & Doyle, P. J. (2014). Description of an intensive residential aphasia treatment program: Rationale, clinical processes, and outcomes. *American Journal of Speech-Language Pathology*, *23*, S330–S342. doi:10.1044/2014_AJSLP-13-0102