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Auditory, Phonological and Semantic Factors in the Recovery from Wernicke's Aphasia Post Stroke: Predictive Value and Implications for Rehabilitation

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Figures & Tables:

Two tables

Three figures, all colour

Abstract:

Background: Understanding the factors that influence language recovery in aphasia is important for improving prognosis and treatment. Chronic comprehension impairments Wernicke's-type aphasia (WA) are associated with impairments in auditory and phonological processing, compounded by semantic and executive difficulties. This study investigated whether the recovery of auditory, phonological, semantic or executive factors underpins the recovery from WA comprehension impairments by charting changes in the neuropsychological profiles from the sub-acute to the chronic phase.

Method: This study used a prospective, longitudinal, observational design. Twelve WA participants with superior temporal lobe lesions were recruited before 2 months post stroke onset (MPO). Language comprehension was measured alongside a neuropsychological profile of auditory, phonological and semantic processing alongside phonological short-term memory and nonverbal reasoning at three post stroke time points: 2.5, 5 and 9MPO.

Results: Language comprehension displayed a strong and consistent recovery between 2.5 and 9MPO. Improvements were also seen for slow auditory temporal processing, phonological short-term memory, and semantic processing, but not for rapid auditory temporal, spectrotemporal and phonological processing. Despite their lack of improvement, rapid auditory temporal processing at 2.5MPO and phonological processing at 5MPO predicated comprehension outcomes at 9MPO.

Conclusions: These results indicate that *recovery* of language comprehension in WA can be predicted from *fixed* auditory processing in the subacute stage. This suggests that speech comprehension recovery in WA results from reorganisation of the remaining language comprehension network to enable the residual speech signal to be processed more efficiently, rather than partial recovery of underlying auditory, phonological or semantic processing abilities.

Key Words: stroke recovery, neuroplasticity, reorganisation, auditory comprehension, aphasia

Introduction:

Wernicke's aphasia (WA) is a syndrome resulting in severe disruption to language production and comprehension. WA results from lesions to the left temporoparietal region [1–3] which supports a range of functions related to language comprehension including auditory and phonological processing of the speech stream in the superior temporal lobe [4–7], semantic processing of lexical information in the middle temporal and angular gyri [8–11] and short-term phonological memory relevant for syntactic comprehension in the supramarginal gyrus and posterior superior temporal lobe [12–14]. WA occurs in 20% of acute aphasia presentations but reduces to 5% by the chronic phase [15]. Despite this, persistent WA has proved resistant to therapeutic intervention [16,17]. Detailed consideration of the evolution of neuropsychological processes during recovery from WA will increase our understanding of the mechanisms of post-stroke plasticity in the left hemisphere language system and contribute to informing accurate prognosis and the development of effective rehabilitation.

The neuropsychological profile observed in *chronic* WA displays impairments which mirror the function of the left temporo-parietal regions identified through neuroimaging studies (i.e., auditory-phonological processing, phonological short-term memory and semantics) [2,18–20]. The areas most consistently affected by lesion in WA are the left mid-posterior superior temporal gyrus (STG) and sulcus (STS) and underlying white matter [1,3,20]. These regions are associated with the analysis of acoustic stimuli, including stimuli with relative simple acoustic structures such as modulated tones, frequency sweeps and harmonic stimuli [21–23] as well as with the analysis of auditory-phonological information [24,25]. Patients with chronic WA display impairments in detecting and analysing auditory stimuli with all but the most simple acoustic structures (e.g. pure tones) [19] and have severe difficulties in discriminating phonological differences in word and non-word stimuli [3,18]. Importantly, we have previously demonstrated a direct link between auditory and phonological processing abilities and language comprehension [19,26], supporting the hypothesis that impaired speech comprehension in WA is a consequence of deficits in hierarchical auditory processing leading to underspecified or noisy access to semantic information [27–29]. Lesions in WA commonly spread beyond this core region into the middle temporal (MTG) and/or angular gyri (AG), associated with a range of cognitive functions including lexical and semantic processing [11,30]. Concurrently, across the WA population, semantic processing is usually but not universally impaired [3]. Although no statistical relationship between semantic abilities and language comprehension has been documented in chronic WA, it is logical that semantic impairments compound the speech perception based comprehension deficits. One further area frequently affected in WA is the supramarginal gyrus (SMG). Lesions to this region are associated with impairments of phonological encoding during speech production [31,32], however, functional neuroimaging and lesion-symptom mapping indicates that the SMG and posterior STG are part of a network supporting auditory and phonological short term memory [12,33,34], a cognitive function associated with the comprehension of sentence and discourse-level information [35].

At present, relatively little information exists concerning the cognitive neuropsychological profile of *acute* WA and how this evolves over time. Based on the neuropsychological profile observed in chronic WA it was hypothesised that recovery of comprehension in WA would be supported by the recovery or improvement of underlying cognitive functions, in particular auditory-phonological analysis known to impact comprehension at the chronic stage. More specifically, it was hypothesised that improved scores on auditory and phonological analysis tasks would precede or parallel improvements in language comprehension. To investigate this hypothesis, we present here the first longitudinal prospective neuropsychological study exploring the cognitive dynamics underpinning changes in WA-type comprehension impairments from the sub-acute through to the chronic stage.

Methods and Materials:

Study Design: This study comprised a longitudinal cohort observational study. Participants with Wernicke's-type aphasia were recruited in the acute-subacute phase (0-2 months post onset, MPO). Longitudinal neuropsychological assessments were undertaken three times at 2.5, 5 and 9MPO. Ethical approval was granted by the NHS Research Ethics Committee (REC ref: 13/EE/0014), all participants gave written informed consent.

Study Setting: Participants were recruited from NHS in-patient services in the south of England with the support of local clinical and research teams. The recruitment period extended from April 2013 to February 2016. Following referral participants were screened for eligibility and invited to take part in the study. All screening and data collection visits occurred in the participants' homes. Data collection at each time point was collected over multiple sessions, 3-5 depending on the participant, and collection was completed within 2.5 weeks.

Participants: Participants were referred to the study by NHS research practitioners or speech and language therapists if they presented with any error on a single word language comprehension screening assessment and any error on a single word repetition screening assessment. Screening assessments were developed in-house for the purpose of the study. Participants or friends/relatives/carers provided written consent/assent for referral. A total of 24 participants were referred to the study of which 17 were contactable and 12 fulfilled the inclusion and exclusion criteria and consented to participate. One participant (pt 7) was referred too late to be included in the first testing time point (2.5 MPO), all remaining participants took part in all testing time points. Participants were considered eligible for the study if they presented with the classical dimensions of Wernicke's aphasia – fluent speech, impaired comprehension, impaired repetition – or if they displayed differential performance on spoken and written word comprehension assessments with spoken comprehension being disproportionately impaired in comparison to written word comprehension, consistent with previous reports of WA. Screening assessment used the Boston Diagnostic Aphasia Examination – Short Form [36]. Although the phonological paraphasias that hallmark WA were not an inclusion criteria, these were nevertheless observed in all participants. Participants were excluded if there was a significant history of previous neurological disorder, including previous stroke with the exception of TIAs.

Twelve individuals were recruited to the subacute group, 10 displayed classical Wernicke's aphasia at the point of recruitment and 2 displayed a non-classical profile with reduced fluency contributed to by severe apraxia of speech (pt 9 and 12). Table 1 presents an overview of participant demographics and neuroimaging. All participants were right handed with the exception of participant 2 and all participants were monolingual English speakers.

Table 1 about here

Participant Neuroimaging: Where possible, 3T MRI structural T1-w images were collected for lesion definition at the Centre for Integrative Neuroscience and Neurodynamics at the University of Reading. Data were collected on a GE x750 3.0 Tesla MRI Scanner with a 12 channel head coil. An MPRAGE sequence with 2 averages: 192 slices, $1mm^3$ resolution, 250mm FOV, TR 2020ms, TE 302ms, Inversion Time 900ms. Clinical neuroimaging data (CT or MRI) were obtained for participants with significant contraindication to MRI or who declined an MRI scan. Three of these participants' CT scans did not show any clear evidence of lesion and were not included in further imaging analysis.

Lesions were delineated manually using lesion drawing in native space on a slice-by-slice basis in MRIcron [37]. The SPM Clinical Toolbox [38] was used for scan and lesion normalisation. Scans were normalised to a CT or MRI template using cost-function masking and normalisation parameters were subsequently applied to the native space lesion image.

Subsequently binary lesion images were compared to normalised scans and modifications were made to the lesion images where necessary.

The lesion overlap map is displayed in Figure 1. Overall, the group displayed a relatively homogeneous lesion distribution with high overlap in the white matter of the left superior temporal lobe. There was maximal overlap in the mid-posterior superior temporal gyrus, high overlap in temporoparietal junction regions (superior temporal sulcus, middle temporal gyrus) and involvement of the anterior superior temporal sulcus in half the group.

Figure 1 about here

Neuropsychological Measures/Variables

Primary outcome variable: This study used a composite score from two auditory comprehension assessments as the primary outcome measure. These assessments were the Boston Diagnostic Aphasia Examination (BDAE) auditory comprehension subtests (single word, phrases and complex ideational material) and an in-house six distracter single spoken-word picture matching (sWPM) assessment consisting of 48 items of varying familiarity and phonological length. Frequency and imageability were controlled across all trials of the sWPM test. Distracters comprised of an item semantically related to the target, phonologically related to the target, phonologically related to the semantic distracter and two unrelated distracters. The sWPM test was administered in eprime, recorded spoken words were played over headphones and the participant pointed to the picture they believed to correspond to the word. Table 1 displays normal cut-off data for this assessment and the other neuropsychological assessments based on data from 15 neurotypical individuals aged 50-82. Normal cut-off was defined as the mean score minus two standard deviations. A composite comprehension measure was derived because of the high correlations between the BDAE and sWPM measures at 9MPO (r^2=0.76; p=0.004), to produce a variable more reflective of the data from research into chronic WA which focuses on the single word level and to reduce multiple comparisons. The composite score was created using unrotated principal component analysis which produced a single factor with an eigenvalue greater than 1.

Neuropsychological Measures/Explanatory Predictors: Neuropsychological measures of component linguistic abilities (auditory, phonological, cognitive-semantic processing) were administered to explore the degree to which they were able to predict comprehension recovery.

Auditory processing:

Auditory processing assessments were selected to reflect the known impairment profile in chronic WA[19]. Rapid and slow auditory temporal modulation processing was measured using 40Hz and 2Hz frequency modulation (FM) detection, respectively. Spectrotemporal modulation processing was measured using dynamic modulation (DM) "ripple" detection. FM was applied to 500Hz carrier tones. DM stimuli consisted of 400 frequency components, logarithmically spaced across four octaves from 250 to 4000Hz modulated with an upward drift at a rate of 1cycle/octave, -4cycles/second. Threshold modulation index (FM) and modulation depth (DM) at which modulation could just be detected was calculated through adaptive staircase paradigms. The adaptive staircase paradigms used a three interval, two alternative forced choice AxB two-down, one-up design. Participants heard three stimuli and were instructed to identify which was the "odd-one-out" or which stimulus was "wobbly" by pointing to a sheet of paper with boxes representing the trial structure. The target stimulus was never in the middle position which acted as a reference. The assessment consisted of 40 trials starting at supra-threshold modulation index/depth. Each trial was 3750ms in length (three stimuli and two ISI of 750ms). After two consecutive correct responses the modulation index/depth was decreased and after one incorrect stimulus the modulation index/depth was increased – a reversal. Thresholds were calculated as the average of modulation index/depth of the final 6 reversals. Auditory processing experiments were administered using Matlab R2013a. The adaptive staircase design reduces memory and language load and enables the experimenter to observe whether task instructions have been comprehended as a staircase pattern cannot be achieved by guessing[19].

Phonological processing:

Input phonological analysis was measured using non-word phonological discrimination[18], word phonological discrimination and phonological short term memory. Non-word discrimination used an in-house test of non-word discrimination based on phoneme confusability[39]. The experiment consisted of 14 levels (level 14 = easiest, level 1 = hardest) in which the stimuli systematically varied by the degree of phoneme confusability between reference and target stimuli. On levels 14-5 both the first and final phoneme differed between the reference and target and on levels 4-1 only the final phoneme differed. The experiment started at level 14 and used a three-down, one-up design. Each trial used a three interval, two alternative forced choice AXB structure and participants were required to respond non-verbally. The test was terminated after 8 reversals or 8 consecutive correct responses at level 1. Threshold was calculated as the average level at which the final four reversals occurred. Phonological discrimination was measured using an in-house 48 item AXB test. Within each trial items were matched on imageability, frequency and familiarity. Items differed by a single phoneme word initially, medially or finally (e.g. word initial: parrot, parrot, carrot). Discrimination accuracy was taken as the raw score. Non-word phonological discrimination and word phonological discrimination were presented in E-Prime version 2.0. Phonological short-term memory was measured using for immediate forward digit span recall from the Wechsler Memory Scale- Revised [40]. Each correct response was given a score of 1, with a maximum score of 2 for each span length (max. score 14).

Semantic & cognitive processing:

Semantic processing was measured using the 32-item version of the Camel and Cactus semantic association test[41]. Each trial consisted of this paper based assessment presents a picture probe stimulus at the top of the page and four inter-related picture stimuli below (one target, three distracter). The participant is required to identify which stimulus is related to the probe stimulus (e.g. Probe: camel; Target: cactus; Distracters: sunflower, rose, tree). Semantic processing accuracy was taken as the raw score. Nonverbal reasoning was measured using Raven's Colour Progressive Matrices[42] and age-related centile rank was derived from the raw score.

Additional Variable: Peripheral Hearing: Alongside age and time post onset, bilateral pure tone peripheral air conduction hearing thresholds at 0.5, 1, 2, & 4kHz were measured and averaged.

Bias: Potential bias in the study may have arisen through recruitment procedures e.g. only more capable and medically well individuals being referred to the research. A consultee referral mechanism was available as an attempt to mitigate against this.

Study Size: An a priori power calculation using correlation effect size from Robson et al., (2012) indicated that n=12 provided a 92% probability of identifying significant relationships between neuropsychological assessment and comprehension outcome measures.

Results

Recovery: Improvements in language comprehension and neuropsychological profile were investigated using one-way ANOVA (time points 2.5, 5 & 9 months) and are displayed in Figures 2-3, raw data can be found in Tables 2-4. A significant improvement in comprehension over time was found (BDAE: $F(2,20)=22.2$, $p<0.001$, eta = 0.69; sWPM: $F(2,20)=34.5$, $p<0.001$, eta = 0.78, Figure 2). Across the case series, all but one participant displayed improvements in language comprehension from 2.5 to 9MPO. Post-hoc paired t-tests showed that significant improvements were made between 2.5 and 5MPO and 5 and 9MPO for both assessments (BDAE $t_{(11)}>3.2$; sWPM $t_{(11)}>5.2$ for all pairwise comparisons) . Comprehension scores from the BDAE and sWPM were correlated at the final time point ($r^2=0.76$; $p=0.004$) and, therefore, were combined into a single comprehension measure using unrotated principal component analysis for further correlation analyses.

Significant improvements over time were found in auditory, phonological and semantic processing (Figure 3): slow auditory temporal processing (2Hz frequency modulation detection; $F(2,12)=4.3$, $p=0.039$, eta=0.42), phonological short-term memory (digit-span score; $F(2,20)=8.3$, $p=0.002$, eta=0.45) and semantic association (Camel and Cactus Test; $F(2,20)=4.7$, $p=0.021$, eta=0.32), however it is important to note that improvements were not seen across the remaining neuropsychological tasks. Paired t-tests found that the phonological short term memory significantly improved between all three time points ($t(11)>2.2$) whereas semantic association only improved between 2.5 and 9MPO ($t(10)=2.6$, $p=0.028$) and 5 and

9MPO (t(11)=2.2, p=0.049) and slow auditory temporal processing only displayed a weak improvement between 2.5 and 9MPO (t(6)=2.3, p=0.065) but between no other pairs of time points. A number of individuals fell within normal limits on neuropsychological measures at 2.5MPO, Table 2. The ANOVAs were re-run including only those participants who fell outside normal limits at 2.5MPO; the results remained statistically the same.

Tables 2-4 about here

Figure 2 about here

Within Time Point Correlations: The relationship between language comprehension and underlying cognitive skills overtime was examined with Pearson correlations between neuropsychological and comprehension scores. Tables 2-4 display language comprehension assessments and neuropsychological data across the case series and time points. Unlike in chronic WA, no significant relationships were found between comprehension scores and neuropsychological profile at 2.5MPO. At 5MPO a significant correlation was found between comprehension and phonological processing (word phonological discrimination: r=0.67, p=0.018, p=12), rapid auditory temporal processing (40Hz FM detection: r=-0.69, p=0.012, n=12) and nonverbal reasoning (RCPM: r=0.6, p=0.03, n=12). The correlation between comprehension and rapid auditory temporal processing (40Hz FM detection: r=-0.88, p<0.001, n=11) remained significant at 9MPO.

Figure 3 about here

Correlation with Additional Variables: Onset severity and age have been shown to influence recovery from stroke [43]. Pearson correlations explored the relationship between comprehension scores at 9MPO and additional variables: comprehension score at 2.5MPO, age, average bilateral peripheral hearing threshold and lesion volume in voxels. A significant correlation was found between 2.5MPO and 9MPO comprehension scores (r=0.73, n=11, p=.011) but not age, hearing or lesion volume. As such, comprehension at 2.5MPO was added as a covariate in further correlations.

Cross-Lagged Correlations: The relationship between earlier neuropsychological assessments and later language comprehension was assessed with partial correlations covarying for comprehension scores at 2.5MPO to explore the extent to which the additional cognitive measure could improve outcome prediction beyond that obtained from initial severity. No neuropsychological score at 2.5MPO was significantly associated with comprehension at 5MPO. Rapid auditory temporal processing (40Hz FM detection r=-0.94, df=6, p=<0.001) and phonological short-term memory (digit span r=0.64, df=8, p=0.046) at 2.5MPO were significantly associated with comprehension at 9MPO. Word phonological processing at 5MPO was significantly associated with comprehension at 9MPO (r=0.84, df=8, p=0.002) and a further marginally significant association was found between nonword phonological processing at 5MPO and comprehension at 9MPO (r=-0.63, df=8, p=0.053).

Discussion:

This study aimed to investigate the cognitive dynamics associated with recovery from Wernicke's aphasia (WA) comprehension impairments from the subacute to the chronic phase. Strong recovery in language comprehension was observed indicating considerable functional reorganisation. Analysis of evolving neuropsychological profiles indicates, contrary to the hypothesis, that this reorganisation process is influenced by residual auditory processing capacity (rapid auditory temporal and phonological processing) but does not require the improvement of these abilities. These results suggest that spontaneous recovery of comprehension in WA is dependent on enhancing the efficiency with which the remaining information from the speech signal is employed within the language system. Furthermore, these results indicate that individuals with significant impairments in auditory and phonological abilities at 2.5-5 months post onset (MPO) are at risk for poor language comprehension outcomes.

At the sub-acute stage post stroke onset (2.5 MPO), no relations were identified between language comprehension in WA and any other tested cognitive domain – auditory, phonological or semantic-executive processing. Psycholinguistics, computational modelling and functional neuroimaging have identified these factors to be fundamental to language comprehension. These results, therefore, indicate that the language comprehension network remains highly disorganised into the sub-acute phase, with considerable reorganisation yet to occur. Towards the chronic phase, significant relationships emerged between phonological and auditory processing capacity and language comprehension. At 5MPO, the capacity to discriminate between spoken words as well as the ability to detect rapid auditory temporal modulations was associated with language comprehension, the latter remaining a significant factor at 9MPO. These results indicate an increasingly systematic organisation of the language comprehension network emerging over the first year after stroke and moving towards a pattern established at the chronic phase. Data from individuals with chronic WA indicates the degree of impairment in spoken language comprehension is associated with residual capacity to process phonological and acoustic stimuli [19,26,29]. These results converge with the original model of WA [28] which postulates that an impairment in processing the auditory structure of speech (speech perception) disrupts the ability to accurately access semantic representations corresponding to lexical items and syntactic structures.

Although all individuals in this study had residual comprehension impairments at 9MPO, improvements in language comprehension occurred for all but one participant. At the group level, the degree of improvement in language comprehension was similar between 2.5 - 5 MPO and 5 – 9MPO. These recovery curves parallel those identified by Kertesz et al., [43] which indicated a more drawn-out recovery in WA over the first year post stroke in comparison to other types of aphasia. This pattern also contrasts with other types of impairment post stroke, e.g. motor, in which rapid spontaneous recovery in the early phase plateaus after the first 3-6 months [48–50]. One hypothesis is that differences in the time frame of spontaneous recovery reflect the complexity of underlying functional network organisation, with more complex networks engaging in longer periods of recovery [51]. While there are no direct comparisons of network complexity, the posterior superior-middle aspects of the temporal lobe, the areas of greatest lesion overlap in WA (Figure 1), are proposed to be core aspects of the language network [e.g. 52] and are associated with both dorsal and ventral language pathways [e.g. 53]. This experimental evidence, along with lesion studies, indicates that these regions are critical to almost all aspects of language processing and, therefore, may require protracted periods of reorganisation. This finding may be useful for rehabilitation as it indicates an extended window in which to supplement and augment the process of spontaneous recovery and optimise long-term outcomes.

As well as comprehension recovery, this study identified recovery of associated cognitive functions across auditory, phonological and semantic domains. However, in comparison to recovery in comprehension, the improvements in these associated areas were inconsistent across the case series and only occurred significantly at the group level for a subset of the neuropsychological assessments – slow auditory temporal processing (2Hz frequency modulation detection), phonological short-term memory (digit span) and semantic association (Camel and Cactus Test). In contrast, there was a notable lack of consistent recovery in phonological processing (word and nonword discrimination) and auditory processing requiring the analysis of rapid temporal information or spectrotemporal information. It should be noted that some data from auditory assessments were missing due to participants discontinuing these tests. The most striking finding in the current study was that the factors that showed capacity to improve were, for the most part, not related to long-term comprehension outcomes in WA. Comprehension recovery was independent of performance on slow auditory temporal processing and semantic processing. Instead, a significant influence of rapid auditory processing and phonological processing was found on language comprehension at 9MPO. Cross-lagged correlations found that comprehension capacity at 9MPO was associated with rapid auditory temporal processing (40Hz frequency modulation detection) at 2.5 MPO and word phonological discrimination capacity at 5MPO. These correlations indicate that although acoustic-phonological processing has limited plasticity in WA, these abilities play a significant role in shaping the eventual language comprehension outcome and suggest that residual capacity in these areas is an important prognostic indicator for comprehension recovery.

One interpretation of these behavioural results is that language comprehension recovery in WA results from reorganisation processes which enable increasingly efficient use of residual acoustic-phonological processing capacity. Interestingly, despite an apparent lack of natural plasticity in the acoustic-phonological processing network in the current study, the same abilities have been found to be amenable to therapy induced improvement in chronic phase WA and that therapy for acoustic-phonological processing is effective for improving language comprehension when delivered in large-dose [16,65]. Such therapies may be expected to be even more effective in the subacute phase, where natural plasticity is high. Therapy-induced improvement of early auditory processing may therefore result in a greater recovery of language comprehension abilities over time.

There are a number of further factors that could have impacted the profile of results and capacity to identify the relationship between comprehension and underlying cognitive factors. The current study recruited 12 participants with WA. This sample size reflected an a priori power calculation, however, this calculation was conducted on chronic WA data and the sample remains low. It is possible that a larger sample size would have revealed further associations between neuropsychological assessments and language comprehension outcomes and been suitable for statistical analyses able to identify interactions between auditory, phonological and semantic factors. Secondly, involvement in therapy was not an exclusion criteria for the study and could have accounted for some of the variance in the degree and trajectory of comprehension and neuropsychological profile recovery. Therapy engagement was monitored, however, therapy input reflected personalised targets and local service provision, resulting in high variability in therapy content. Half the group received therapy targeting speech production and only one participant received auditory comprehension therapy (participant 12). No participant received an evidence-based dosage of impairment-based therapy [51]. Dosage and treatment specificity are both key principles for promoting neuroplasticity and recovery of the language network [52]. To reflect this, we ranked the participants in terms of the amount of therapy they received, and this was not correlated with comprehension outcomes (see Supplementary Materials for details of this analysis). Therefore, there is no evidence to suggest that speech and language therapy involvement significantly influenced the primary outcome measure in the current study. One further potential source of unaccounted variance in the current study is the degree of neural atrophy or the presence and severity of small vessel disease (SVD). These factors could impact the capacity for reorganisation in the residual neural network. Age is a known risk-factor for atrophy and SVD [53,54] and the participants in this study were on average older than the participants in the majority of aphasia research studies. As such, this may have limited the potential for functional recovery. However, we found no systematic relationship between age and comprehension outcome or degree of comprehension recovery, and general age-related limitations on recovery would not explain the differences in recovery over tasks. It was noted, however, that two of the older participants (3 and 4, 80 and 93 years old, respectively) displayed consistently low scores on the RCPM over the three testing time points, in contrast to two other participants (2 and 11), who showed low RCPM scores at 2.5 MPO but who had considerably improved by 9 MPO. Whilst it cannot be ruled out that age-related cognitive decline was interacting with stroke recovery processes at least in participants 3 and 4, it could not explain the key findings of an association between sub-acute auditory processing and chronic language comprehension.

Conclusions:

This study provides the first longitudinal consideration of the cognitive dynamics of comprehension recovery in Wernicke's Aphasia. The substantial comprehension recovery observed was not consistently related to the component cognitive abilities that also showed improvement. Rather, long-term comprehension outcomes were primarily shaped by remaining auditory-phonological capacity, despite a lack of improvement in these abilities over time. The results indicate that comprehension recovery in Wernicke's aphasia is constrained by residual auditory-phonological capacity but that improvement in auditory-phonological function is not required for language comprehension recovery. Rapid auditory temporal processing in the sub-acute phase was associated with comprehension outcome in the chronic phase, presenting a potential prognostic indicator for individuals with Wernicke's aphasia, clinicians and researchers and a potential target for early rehabilitation.

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Author contributions:

All authors: research design; HR and AMW: data analysis; All authors: report writing.

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Table 1: Participant Demographics

PT	Age	Gender	Ave. Hearing	Imaging Available	Stroke Aetiology	Regions affected by lesion (lesion volume in voxels)
1	71	M	22	Clin. MRI	Aneurysm	STG; STS; a,mMTG; a,mITG, aFG, ATL (1.18E+05)
2	57	M	31	3T MRI	Infarction	STS (7.70E+03)
3	83	F	38	Clin. CT*	Infarction	N/A
4	90	F	57	Clin. CT*	Infarction	N/A
5	88	M	55	Clin. MRI	Haemorrhage	pSTG; pSTS; m,pMTG, m,pITG (4.31E+04)
6	82	M	69	Clin. MRI	Infarction	m,pSTG; m,pSTS; m.pMTG; AG; SMG (1.30E+07)
7	68	M	19	3T MRI	Infarction	STG; STS; m,pMTG; AG; ATL (1.28E+05)
8	74	M	54	3T MRI	Infarction	m,pSTG; m,pSTS; m,pMTG; AG; SMG (6.09E+04)
9	46	M	19	3T MRI	Infarction	a,mSTG; aSTS; ATL; Ins (7.46E+04)
10	93	F	63	Clin. CT*	Infarction	N/A
11	78	F	29	3T MRI	Infarction	STG; pSTS; pMTG; SMG (5.21E+04)
12	53	M	26	3T MRI	Arterial dissection	a,mSTG; STS; MTG; Ins; IFL (1.57E+05)

Age at 2.5MPO. Average bilateral peripheral pure tone air conduction threshold at 0.5, 1, 2, & 4kHz. * indicates that CT scan did not provide sufficient information for lesion delineation. Clinical imaging was collected in the acute phase. 3T MRI imaging was collected between 11 and 12 MPO. STG = superior temporal gyurs; STS = superior temporal sulcus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; FG = fusiform gyrus; Ins = insula; AG = angular gyrus; SMG= supramarginal gyrus; IFL = inferior frontal lobe; a = anterior; m = middle; p = posterior.

Table 2: Comprehension and Neuropsychological Results at 2.5 Months Post Onset

	Comprehension		Auditory Processing			Phonological Processing			Cog-Semantic Processing	
	BDAE centile	sWPM	2Hz FM	40Hz FM	DM	Nonword Discrim.	Word Discrim.	Digit Span Score	Sem. Assoc.	RCPM centile
Max.		*48*				*1*	*48*	*14*	*32*	
Cut-Off	*48*⁺	*44*	*3.46**	*0.12**	*0.18**	*1.5**	*45*	*8*	*26*	
PT										
1	18.3	29	3.62	**0.09**	**0.13**	**1**	**46**	6	24	95
2	16.7	24	NT	NT	**0.17**	10.8	39	0	23	25
3	28.3	36	3.95	1.15	0.41	9.7	44	0	24	50
4	13.3	24	7.7	0.87	0.39	11.4	42	2	17	10
5	8.3	32	5.7	0.14	**0.18**	10.5	37	2	**26**	50
6	23.3	32	1.4	**0.11**	**0.17**	5	38	2	25	95
7	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
8	18	37	6.45	0.24	0.28	11.9	44	2	**27**	75
9	18.3	35	**1.45**	**0.06**	**0.07**	**1**	**45**	0	25	95
10	16.7	37	5.6	**0.06**	0.32	11.5	**45**	6	30	95
11	21.7	35	NT	NT	0.2	7.1	**46**	6	23	25
12	5	41	**3.2**	**0.1**	**0.18**	**1**	**46**	0	**27**	99

PT = participant, BDAE = Boston Diagnostic Aphasia Examination, sWPM = spoken word-picture matching, FM = frequency modulation detection, DM = dynamic modulation detection, Sem. Assoc. = semantic association assessment (Camel and Cactus Test), ⁺ = cut-off for Wernicke's aphasia, * = inverse scale, lower values correspond to better performance, NT = not tested or testing discontinued by participant. **Bold** font indicates within normal limits.

Table 3: Comprehension and Neuropsychological Results at 5 Months Post Onset

	Comprehension		Auditory Processing			Phonological Processing			Cog-Semantic Processing	
	BDAE centile	sWPM	2Hz FM	40Hz FM	DM	Nonword Discrim.	Word Discrim.	Digit Span Score	Sem. Assoc.	RCPM centile
Max.		*48*				*1*	*48*	*14*	*32*	
Cut-Off	*48*[+]	*44*	*3.46**	*0.12**	*0.18**	*1.5**	*45*	*8*	*26*	
PT										
1	33.3	35	**2.2**	**0.09**	**0.1**	**1**	44	**8**	**27**	95
2	11.7	25	**1.88**	0.4	**0.17**	13.8	29	0	24	50
3	48.3	37	5.92	0.19	0.26	10	35	1	21	50
4	21.7	29	6	0.68	0.35	6.5	38	2	19	5
5	26.7	40	4.8	**0.1**	0.2	5.9	38	5	23	90
6	53.3	36	**1.5**	**0.05**	**0.11**	8.7	39	2	**28**	95
7	23.3	40	**0.55**	**0.11**	**0.1**	2.15	**45**	5.5	**26**	95
8	63.3	40	**3.2**	0.14	0.23	9.9	**48**	3	**30**	95
9	25	38	**2.65**	0.14	**0.14**	**1**	42	0	**26**	99
10	50	39	**2.65**	0.16	0.29	9.79	**45**	**10**	**29**	99
11	31.7	40	3.78	**0.08**	0.2	2.3	**46**	5	23	90
12	10	43	**3.25**	0.16	**0.14**	**1**	**47**	2	**27**	99

PT = participant, BDAE = Boston Diagnostic Aphasia Examination, sWPM = spoken word-picture matching, FM = frequency modulation detection, DM = dynamic modulation detection, Sem. Assoc. = semantic association assessment (Camel and Cactus Test), [+] = cut-off for Wernicke's aphasia, * = inverse scale, lower values correspond to better performance, NT = not tested or testing discontinued by participant. **Bold** font indicates within normal limits.

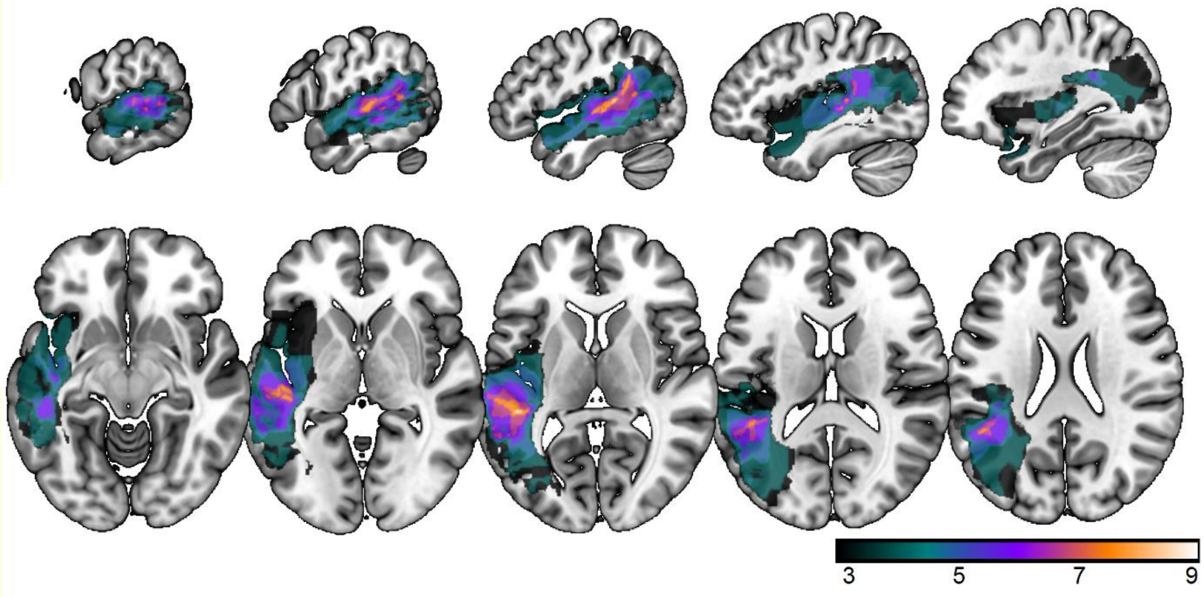
Table 4: Comprehension and Neuropsychological Results at 9 Months Post Onset

	Comprehension		Auditory Processing			Phonological Processing			Cog-Semantic Processing	
	BDAE centile	sWPM	2Hz FM	40Hz FM	DM	Nonword Discrim.	Word Discrim.	Digit Span Score	Sem. Assoc.	RCPM centile
Max.		*48*				*1*	*48*	*14*	*32*	
Cut-Off	*48*[+]	*44*	*3.46**	*0.12**	*0.18**	*1.5**	*45*	*8*	*26*	
PT										
1	50	42	**2.9**	**0.11**	**0.05**	**1**	**48**	**9**	**29**	95
2	15	26	**2.6**	0.23	0.26	3.6	36	0	**31**	75
3	48.3	38	NT	0.2	0.39	5.9	37	2	25	50
4	25	35	**2.25**	0.19	0.39	8.3	41	2	18	10
5	41.7	39	4.5	**0.11**	**0.16**	5.6	42	6	24	90
6	63.3	**44**	**1.7**	**0.09**	**0.18**	7.39	34	4	**28**	95
7	50	**46**	**1.45**	**0.06**	**0.07**	**1**	**46**	7	**26**	95
8	56.7	**44**	**3**	**0.08**	0.22	9.8	40	3	**29**	75
9	45	**44**	**2.1**	0.15	**0.15**	**1**	**45**	0	**29**	99
10	66.7	42	**0.85**	**0.04**	0.26	6.3	43	**9**	**28**	99
11	73.3	**45**	6.65	**0.06**	0.22	7.2	**45**	6	**28**	90
12	33	**46**	NT	NT	**0.15**	**1**	44	2	**28**	99

PT = participant, BDAE = Boston Diagnostic Aphasia Examination, sWPM = spoken word-picture matching, FM = frequency modulation detection, DM = dynamic modulation detection, Sem. Assoc. = semantic association assessment (Camel and Cactus Test), + = cut-off for Wernicke's aphasia, * = inverse scale, lower values correspond to better performance, NT = not tested or testing discontinued by participant. **Bold** font indicates within normal limits.

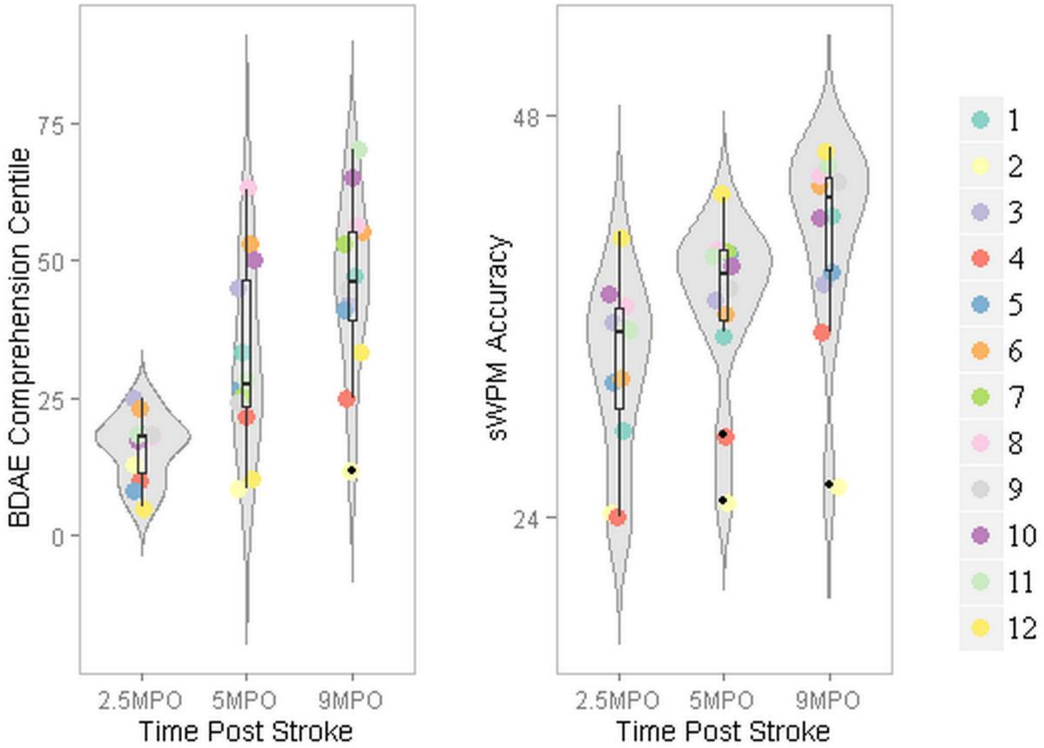
Figure Legends:

Figure 1: Lesion Overlap Map:



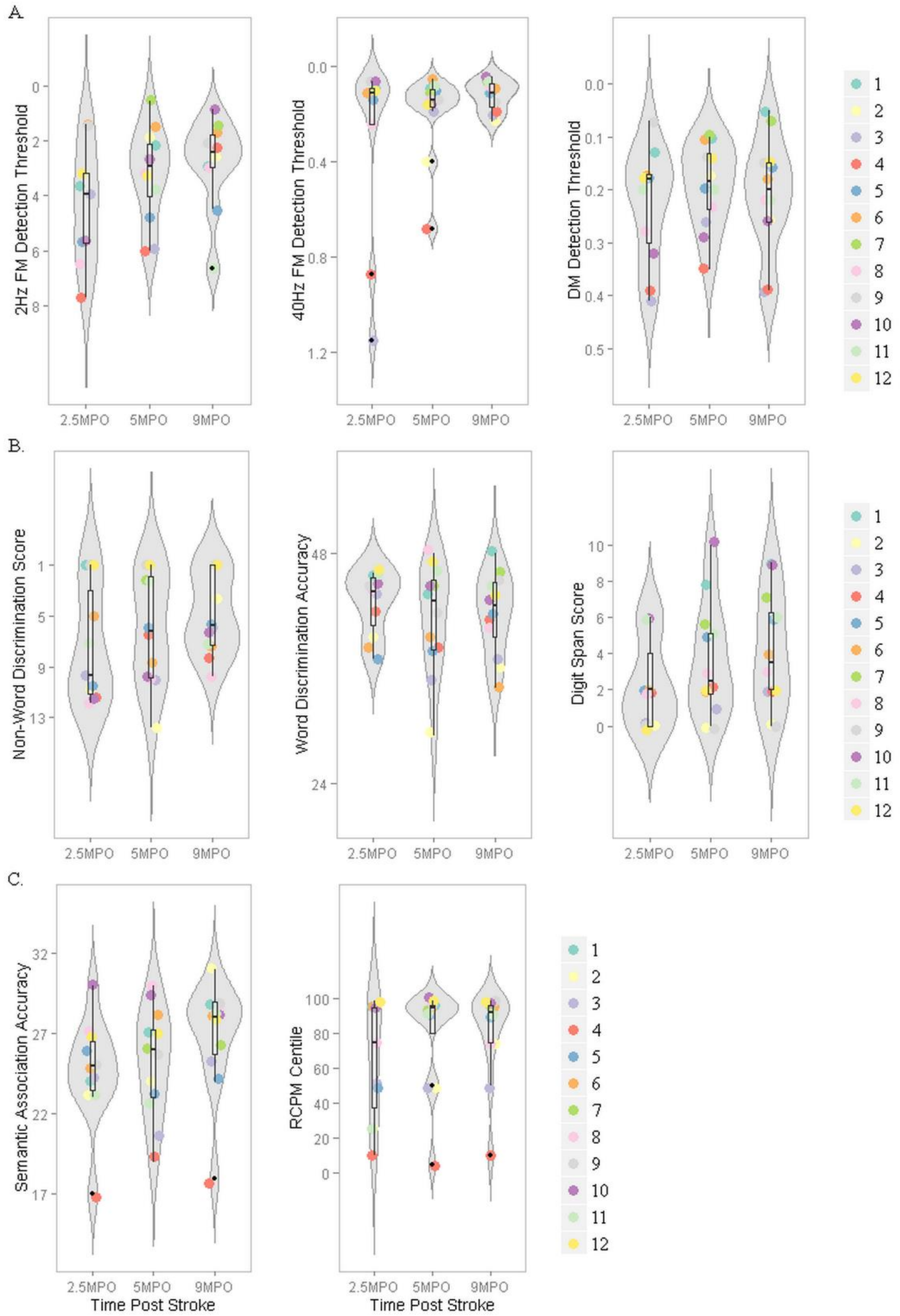
Legend: Lesion overlap map created from binary lesion images from 9 participants. The remaining 3 participants did not have sufficient neuroimaging to identify full lesion extent. The map was created in MRIcron and presented in MRIcroGL. Sagittal coordinates: -61 -54 -47 -40 -33; Axial coordinates: -9 -1 7 15 23. Colour bar indicates number of participants with lesion in each area, maximum potential overlap n=9.

Figure 2: Auditory language comprehension profile:



Legend: Violin, box and dot plots representing group and individual data for auditory comprehension assessments at 2.5, 5 and 9 months post onset. Participants are ordered alphabetically. The thickness of the violin plot represents the probability of a score based on the distribution of the group data. Each dot represents and individual participant's performance, see legend. Box plots represent the mean and distribution of the scores.

Figure 3: Auditory processing, phonological processing and semantic-cognitive processing profile from sub-acute to chronic phase:



Legend: Violin, box and dot plots displaying probability distribution and individual data for auditory processing tasks (2Hz & 40Hz frequency modulation detection and dynamic modulation detection) in panel A, phonological processing tasks (nonword discrimination, word discrimination and digit span) in panel B and cognitive-semantic tasks (semantic association and non-verbal reasoning) in panel C. Data is presented from 2.5, 5 and 9 months post onset. FM = frequency modulation, DM = dynamic modulation, RCPM = Raven's Colour Progressive Matrices. The thickness of the violin plot represents the probability of a score based on the distribution of the group data. Each dot represents and individual participant's performance, see legend. Box plots represent the mean and distribution of the scores.

Auditory, Phonological and Semantic Factors in the Recovery from Wernicke's Aphasia Post Stroke: Predictive Value and Implications for Rehabilitation

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Supplementary Materials

The primary auditory comprehension outcome measure for this study was derived from combining the auditory comprehension sections from the Boston Diagnostic Aphasia Examination Short Form [1] and an in-house test of spoken word to picture matching (sWPM). These supplementary materials detail the properties and content of the sWPM test.

sWPM Test Items

The sWPM test contained 48 items. Each trial presented six items from which the participant was required to select the target that matched the spoken word. The six items consisted of 3 pairs of semantically associated items: a target and an item semantically related to the target; a phonological distracter and an item semantically related to the phonological distracter and two semantically associated distracters unrelated to the target. The unrelated distracters formed target-semantic pairs from other in other trials. Targets were selected based on typicality[2] and phonological complexity. Half the target items were of high typicality (HT: > 5.3 typicality rating) and half were of low typicality (LT <5.3 typicality rating). Half the target items were of high phonological complexity (HP: >3 phonemes, phonological neighbours <10) and half the target items were of low phonological complexity (LP: 2-3 phonemes, phonological neighbours >10). This resulted in 12 HT-HP; 12 HT-LP; 12 LT-HP and 12 LT-LP items. Supplementary Table 1 details the test items and the psycholinguistic properties of the items including frequency and imageability and age of acquisition (where available) sourced from the N-Watch database [3].

Correlations with Established sWPM Tests

As an early exploration of properties of the sWPM task, the sWPM scores were correlated with established word-picture matching tests: The Boston Diagnostic Aphasia Examination (BDAE) [1] and Cambridge Semantic Battery (CSB) [4]. At 2.5 months post onset (MPO) the sWPM test showed a borderline significant relationship with the CSB (r=0.56, p=0.07) but a weak, non-significant relationship with the BDAE (r=0.09, p=0.8). At 5 MPO there was a strong, significant relationship with the CSB (r=0.76, p=0.004) and a moderate, non-significant relationship with the BDAE (r=0.46, p=0.13). At 9 MPO there was a strong, significant relationship with both the CSB (r=0.88, p<0.001) and the BDAE (r=0.77, p=0.004). These results support the reliability of the sWPM test and align with a key finding in study that earlier stages of recovery are associated with less coherence in the language network.

Supplementary Table 1:Psycholinguistic Properties of the sWPM Target and Distracter Items

Item No.	Target									
		Typicality - H/L	Phon. Complexity - H/L	CELEX Freq.	Phon. Len.	Phon. Neighbours	AOA1	AOA2	IMG1	IMG2
1	sandal	H	H	1.06	5	8				
2	trumpet	H	H	4.86	7	2			628	
3	drum	H	H	8.72	4	9		319	599	502
4	lily	H	H	6.7	4	8	317		541	
5	willow	H	H	3.63	4	5	386		565	
6	thrush	H	H	1.28	4	5		368		564
7	trainer	H	H	3.41	6	6	345		602	
8	swede	H	H	0.84	4	9				
9	fridge	H	H	3.91	4	3				
10	beetle	H	H	4.86	4	6				
11	rabbit	H	H	10.78	5	5	206		611	
12	shovel	H	H	4.13	4	4			538	
13	rake	H	L	2.85	3	26	336		550	
14	cap	H	L	30.34	3	29				
15	pear	H	L	2.46	3	22			590	
16	jet	H	L	12.63	3	20			585	
17	pea	H	L	1.68	2	24				
18	peach	H	L	3.02	3	18	292		613	
19	coach	H	L	28.32	3	15	300	346	624	574
20	moth	H	L	2.85	3	12			577	
21	vice	H	L	14.25	3	12	517		413	
22	goat	H	L	11.68	3	19	204	282	636	
23	pine	H	L	13.52	3	27	394		478	
24	horn	H	L	9.27	3	25	308		566	
25	carriage	L	H	12.91	5	6	367		529	
26	rocket	L	H							
27	clippers	L	H	0.56	6	3				
28	mallet	L	H	1.68	5	5	448		533	
29	snail	L	H	2.57	4	8			577	
30	whistle	L	H	9.66	4	5			574	
31	fleece	L	H	0.84	4	4	367		547	
32	trainer	L	H	3.41	6	6	345		602	
33	buggy	L	H	0.84	4	8				
34	badger	L	H	3.69	5	5		359		607
35	beret	L	H	1.79	4	2				
36	frog	L	H	4.41	4	7	258		617	
37	corn	L	L	24.97	3	29	299		580	
38	seal	L	L	12.85	3	23	320	376	607	556
39	yacht	L	L	4.64	3	14	363		624	

40	goose	L	L	6.37	3	11		286		616
41	nut	L	L	6.98	3	20				
42	whale	L	L	6.31	3	37		368		634
43	cod	L	L	9.72	3	31		368		561
44	cape	L	L	15.53	3	21	319		520	
45	cart	L	L	8.83	3	25	258		597	
46	barge	L	L	3.46	3	17				
47	palm	L	L	19.72	3	14	333		555	
48	nut	L	L	6.98	3	20				

	Phonological Distractor									
Item No.		C beg/ C end	N/M/F	CELEX Freq.	Phon. Len.	Phon. Neighbours	AOA1	AOA2	IMG1	IMG2
1	handle	B	N	42.96	5	6	305		525	
2	crumpet	B	N	0.39	7	2				
3	crumb	B	M	1.01	4	11			497	
4	chilli	B	M	0.61	4	6				
5	pillow	B	F	13.8	4	4	217		624	
6	brush	B	F	17.93	4	6	214	198	570	
7	trailer	E	N	3.13	6	8	407		538	
8	sweet	E	N	46.93	4	6		172	493	582
9	fringe	E	M	13.52	5	3	283		500	
10	beagle	E	M	1.06	4	4	594		362	
11	ratchet	E	F	0.89	5	3				
12	shuttle	E	F	10.17	4	4				
13	lake	B	N	40.11	3	27	256		616	
14	tap	B	N	20.5	3	24	222	350	541	
15	hare	B	M	7.15	3	17	281		577	
16	net	B	M	32.35	3	24	269		540	
17	knee	B	F	29.44	2	21	231		597	
18	leech	B	F	1.06	3	21				
19	coat	E	N	52.4	3	28	197		572	
20	moss	E	N	6.37	3	20	354		579	
21	vine	E	M	2.57	3	17	425		564	
22	goal	E	M	29.66	3	26	294		556	
23	pipe	E	F	22.91	3	19	322		617	
24	hawk	E	F	13.35	3	23	400		580	
25	garage	B	N	22.79	5	0				
26	locket	B	N	NA						
27	slippers	B	M	7.82	6	6				
28	pallet	B	M	0.61	5	9	546		425	
29	scale	B	F	73.35	4	13	397		463	
30	thistle	B	F	1.34	4	1	333		624	

31	fleas	E	N	2.23	4	12			
32	trailer	E	N	3.13	6	8	407		538
33	bunny	E	M	1.06	4	11			585
34	banner	E	M	6.82	5	7	368		548
35	berry	E	F	2.46	4	14	289		551
36	froth	E	F	2.18	4	5			
37	pawn	B	N	2.23	3	31			479
38	heal	B	N	4.58	3	24		357	438
39	knot	B	M	7.99	3	25	303		547
40	moose	B	M	0.73	3	16		497	
41	hut	B	F	22.57	3	28			560
42	nail	B	F	12.01	3	29	272		588
43	cog	E	N	0.95	3	18			
44	cake	E	N	21.4	3	24	214		624
45	calf	E	M	10.39	3	14	331	294	559
46	barn	E	M	10.39	3	23	289		589
47	path	E	F	50.84	3	10	269		580
48	nun	E	F	5.36	3	18		409	617

	Semantic distractor								
Item No.		EAT overlap	CELEX Freq.	Phon. Len.	Phon. Neighbours	AOA1	AOA2	IMG1	IMG2
1	shoe	0.28	14.47	2	21	152		640	
2	horn	0.05	9.27	3	25	308		566	
3	guitar	0.02	5.7	5	1	299		645	
4	pond	0.08	14.36	4	14	239		599	
5	reed	0.09	5.47	3	23	369		520	
6	nest		13.74	4	18	282		584	
7	wellington		4.64	8	0				
8	carrot	0.05	2.51	5	6			577	
9	cooker	0.05	3.85	5	4				
10	spider	0.02	4.08	6	3		254	597	
11	weasel		1.34	4	4		458		518
12	axe		5.64	3	19	311		597	
13	hoe	0.16	2.85	2	30				
14	feather	0.02	0	-					
15	plum	0.04	2.91	4	10			611	
16	rocket	0.01	8.1	5	7			612	
17	bean	0.04	3.8	3	18			538	
18	fig	0.03	5.36	3	15				
19	truck		24.8	4	9	261		590	
20	caterpillar	0.04	0	-					
21	chisel		2.12	4	2			567	

22	pig	0.02	17.88	3	18	233		635	
23	logs		4.08	4	16				
24	flute		2.51	4	13			581	
25	cart	0.06	8.83	3	25	258		597	
26	astronaut	0.07	0.95	8	1				
27	scissors	0.07	4.41	5	3			609	
28	axe	0.02	5.64	3	19	311		597	
29	slug	0.08	2.23	4	14				
30	flute	0.02	2.51	4	13			581	
31	lamb	0.05	19.44	3	26	186		614	
32	stiletto		0.34	7	0				
33	pram		5.31	4	8	197		612	
34	mole	0.05	3.85	3	26			567	
35	blazer	0.33	3.74	6	2	470		499	
36	lily	0.01	6.7	4	8	317		541	
37	wheat	0.05	29.44	3	19	386		577	
38	otter	0.04	9.33	4	11	383		572	
39	anchor	0.01	6.2	5	7	387		620	
40	duck	0.03	10.95	3	25	164		632	
41	bolt	0.15	9.72	4	13	369		551	
42	shark	0.08	13.74	3	15	252		645	
43	chips	0.05	10.56	4	19				
44	gown	0.04	9.39	3	9		410	578	580
45	donkey	0.02	9.05	5	2		235		631
46	canoe	0.01	3.74	4	1	394		602	
47	coconut	0.07	2.23	7	1				
48	acorn	0.02	0.56	4	0				

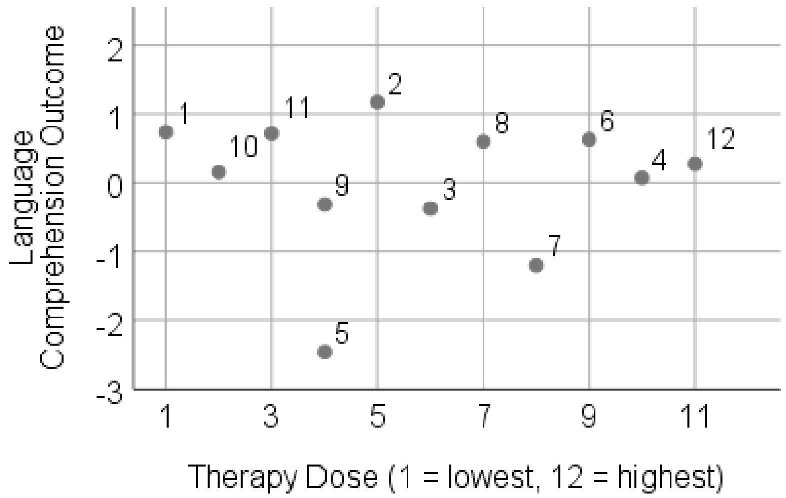
Item No.	Semantically Related to Phonological Distractor	EAT overlap	CELEX Freq.	Phon. Len.	Phon. Neighbours	AOA1	AOA2	IMG1	IMG2
1	broom	0.12	6.48	4	10	313		595	
2	toast	0.12	14.53	4	12		364	594	556
3	biscuit	0.05	4.92	6	3			571	
4	pepper		6.82	5	7	269		587	
5	feathers	0.04	15.87	5	5				
6	mop	0.04	4.08	3	19		331		502
7	tractor	0.73	6.87	7	1	240		655	
8	sweet	0.04	1.34	3	9	278		567	
9	moustache		12.68	6	0				
10	fox		13.74	4	17	283		607	
11	spanner		0.73	6	4				
12	glider		1.79	6	1				

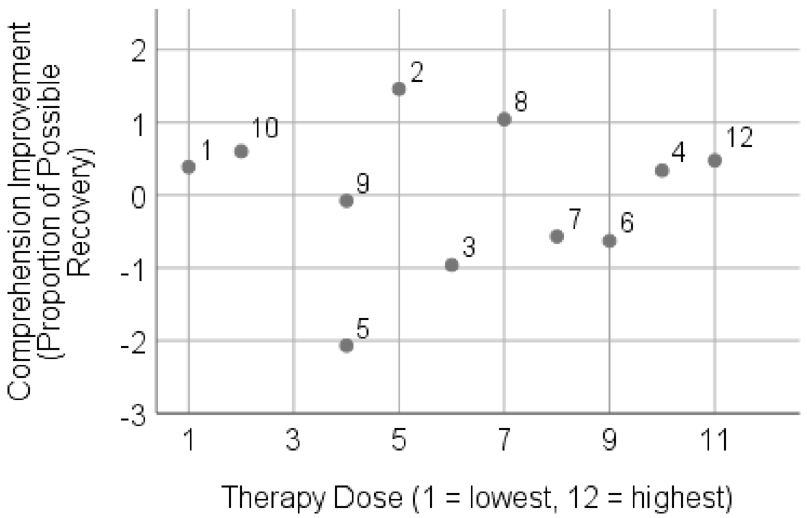
13	river	0.03	108.27	5	9	214	260	608	
14	sink	0.03	26.2	4	17	244	236	611	547
15	tortoise	0.14	3.97	5	0		331	539	
16	pond		14.36	4	14	239		599	
17	elbow	0.09	15.64	4	2	237		602	
18	slug		2.23	4	14				
19	hat	0.22	53.07	3	36			562	
20	fern	0.05	2.29	3	21				
21	grapes	0.07/0.35	7.93	5	9				
22	football	0.16	32.01	6	1	233		597	
23	cigar	0.01	13.02	5	1	439		644	
24	robin		11.56	5	2	233		615	
25	shed	0.08	23.18	3	21	231		602	
26	necklace	0.05	2.29	6	2			606	
27	pyjamas	0.04	7.21	7	1				
28	easel		1.9	3	5			532	
29	weight	0.07	92.96	3	26	333		373	
30	roses	0.02	15.14	5	6				
31	moth	0.01	2.85	3	12			577	
32	tractor	0.73	6.87	7	1	240		655	
33	carrot		2.51	5	6			577	
34	flag	0.44	19.89	4	11	258		607	
35	holly	0.06	1.84	4	15				
36	bubble	0.04	4.19	4	10	272		604	
37	chessboard		0.56	6	0				
38	toe	0.02	9.61	2	27	194		620	
39	string	0.07	22.74	5	6	243		620	
40	deer		11.68	3	20	281		624	
41	tent		36.7	4	20	283		593	
42	hammer	0.32	12.57	5	5	274	297	668	552
43	clock		35.59	4	17	210		640	
44	jam	0.03	13.24	3	18			569	
45	goat	0.01	11.68	3	19	204	282	636	
46	windmill		6.54	6	1				
47	motorway		6.54	6	1				
48	spire		5.31	5	4	438		483	

Supplementary Table 1 Legend: Typicality H/L = high or low typicality; Phonological Complexity H/L = high or low phonological complexity; CELEX freq. = CELEX frequency; Phon. Len. = number of phonemes; Phon. Neighbours = number of neighbours; AOA1/2 = age of acquisition rating 1 [5,6] and 2 [7]; IMG1/2 = imageability ratings 1 [6] and 2 [7]; C beg/C end = phoneme change at the beginning/end of the word; N/M/F = description of whether the phoneme change was a near, medium or far distance from the target corresponding to 1,2 or 3 distinctive features, respectively; EAT overlap = semantic distance between items derived from the Edinburgh Associative Thesaurus.

Correlations with Therapy Dosage

To investigate the relationship between comprehension outcome/recovery and therapy dose, participants were ranked from lowest to greatest time in therapy/therapy dose. As therapy content was highly individual, this raking was independent of type of therapy (e.g. impairment-based vs. functional) and therapy target (e.g. speech production vs. reading comprehension). Pearson correlations were performed between therapy dose and language comprehension outcome at 9 MPO (ρ=-0.193, p=0.55) and proportion of possible improvement on language comprehension tasks (ρ=-0.06, p=0.87). Below are scatter plots displaying these relationships.





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