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Are you a doctor? … *Are you a doctor? I'm not a doctor!* A reappraisal of mitigated echolalia in aphasia with evaluation of neural correlates and treatment approaches

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ABSTRACT

Background: Mitigated echolalia (ME) is a symptom of aphasia which refers to a seemingly deliberate repetition of just-heard words and phrase fragments. ME has historically been viewed as a compensatory strategy aimed to strengthen auditory comprehension. Nevertheless, this hypothesis and other possible functional deficits underlying ME have not been evaluated so far.

Aims: This study aimed to (a) reappraise ME in the frame of modern neuroscience; (b) report the effects of Constraint-Induced Aphasia Therapy (CIAT) and a cognition-enhancing drug (memantine) on detrimental ME in a patient (CCR) with fluent aphasia; and (c) analyse the functional and structural brain correlates of ME in CCR with multimodal neuroimaging.

Methods & Procedure: Tasks tapping verbal expression and auditory comprehension were administered to CCR to evaluate ME. After baseline testing, evaluations were performed under placebo alone (weeks 0–16), combined placebo with CIAT (weeks 16–18), placebo treatment alone (weeks 18–20), washout (weeks 20–24) and memantine (weeks 24–48). Instructions to reduce ME during CIAT were provided to CCR. Language evaluation and multimodal neuroimaging were also performed 10 years after ending treatment.

Outcomes & Results: At baseline, ME occurred in spontaneous speech and in difficult-to-understand single words, indicating impaired meaning access. However, more instances of ME were heard in sentence comprehension, reflecting additional impairment in short-term memory. ME also occurred in words that were correctly defined and understood to the extent that even after accessing word meaning successfully, CCR repeated the same word several times, suggesting impaired inhibitory response control. In comparison with baseline, analysis of auditory sentence comprehension under treatment revealed significant decrements of ME just after ending CIAT and 2 weeks later. These gains were

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maintained under memantine 6 months later. No changes in ME were found during both placebo and washout phases. Instructions to constrain ME reduced the time to complete a sentence comprehension task 2 weeks after CIAT. ME returned to baseline levels 10 years later. Multimodal imaging suggested that ME in CCR resulted from residual activity of remnants of the left dorsal stream and the intact right white matter tracts after extensive damage to the left ventral stream.
Conclusions: ME in CCR interfered with functional communication, and it may be attributed to deficits in sound-meaning mapping, auditory short-term memory, attentional control, and inhibition of repetition mechanisms. Our preliminary evidence suggests that ME, in patients like CCR, may be modulated with specific instructions during aphasia therapy and drugs.

In healthy subjects, unintentional imitation of speech and language features (accents, words, expressions) produced by others improves spoken language comprehension and facilitates social interaction (empathy and affiliation between interlocutors) (Adank, Hagoort, & Bekkering, 2010; Delvaux & Soquet, 2007). While imitative behaviour enriches "cultural learning" (Heyes, 2012), inhibition of imitation in everyday life is also necessary for resisting inappropriate stimulus-bound responses (e.g., echoing words and sentences) (Mesulam, 2008). These inhibitory mechanisms ensure that imitative behaviour is goal-directed rather than impulsive and prevent the execution of strong but contextually inappropriate responses (Brass, Ruby, & Spengler, 2009). The situation is different in patients with brain damage who may be captured by different environmental stimuli that automatically trigger inappropriate verbal and motor responses (echophenomena)[1] (Ford, 1989). Echolalia is a major form of echophenomena that is defined as the impulsive and noncommunicative repetition of words and/or utterances spoken by another person, often observed in the absence of the understanding of their meaning (Brain, 1965, p. 105). Despite its original definition, echolalia may not be always automatic, as it may lie in a continuum from being automatically produced (with or without awareness) to a more voluntary and better monitored repetition.

Mitigated echolalia

Mitigated echolalia (ME) represents a less severe variant of echolalia that refers to any language change in the echoed emission for communicative purposes (Pick, 1924). This traditional definition of ME apparently placed it just in the middle of an automatic-voluntary continuum. Nevertheless, this argument is still elusive, because no formal studies on the nature of ME have been done so far. Early accounts (Stengel, 1947) contended that ME facilitates auditory comprehension in patients with receptive language deficits and that it is mainly observed during conversation and less frequently when the patient is engaged in tasks. These clinical observations reported that when patients do not understand the meaning of certain words, they may either reproduce linguistic intonational pattern of questions verbatim (e.g., "Have you got any children?" → "Children? I am not married" – Stengel, 1947, p. 603) or change it

(e.g., "What is your name?" → "My name! Charles Frederick Leale" – Symonds, 1953, p. 4). In ME, entire sentences may be echoed, but more commonly only words or phrase fragments that sound ambiguous, equivocal or are poorly understood are echoed. Most recent descriptions of patients with ME suggest that the number of times the persons with aphasia and ME repeat verbal stimuli (words, phrases) is variable and possibly depends on difficulties in understanding their meaning and impaired short-term memory (Kohn & Friedman, 1986). In a case of word-meaning deafness,[2] the patient (Dr. O) repeated several times a hard-to-define word, whereas he only repeated a word once when he was able to understand and define it correctly (Franklin, Turner, Lambon Ralph, Morris, & Bailey, 1996). For example, the word "slow" was incorrectly defined as: "slow, slow, slow, slow, I know what it is but I can't get it, slow, slow", whereas the word "spare" was incorporated in the response and elicited the correct response "a spare is something more than you actually need" (see Table 4 in Franklin et al., 1996 and similar examples in Kohn & Friedman, 1986). The incessant repetition of the same word in a case just mentioned (Kohn & Friedman, 1986) suggests that ME may be caused by abnormal monitoring due to incompetent response inhibition and unawareness of the number of times that the stimulus is repeated.

Although some authors consider that ME and allied phenomena (echo-answer and contamination)[3] are very frequent in aphasia (Lebrun, Rubio, Jongen, & Demol, 1971), the interest in this topic has waned since the original descriptions (Pick, 1924; Stengel, 1947). Moreover, ME has rarely been described using this label, which makes it hard to find relevant data on this symptom. The little attention paid to ME is reflected in the paucity of reports. Indeed, a literature search in two databases (PubMed and PsycInfo, last search, July 2016) using the keyword "mitigated echolalia" only retrieved seven hits, four of them alluded to autism spectrum disorders and four citations were duplicated. Nevertheless, in a review of individual cases of aphasia (not listed in databases as ME), we found that although the label of ME was not explicitly mentioned, this phenomenon has been described in cases of fluent aphasia, including transcortical sensory aphasia, Wernicke's aphasia, conduction aphasia, anomic aphasia and word-meaning deafness (Berthier, 1995; Bormann & Weiller, 2012; Franklin et al., 1996; Kohn & Friedman, 1986) as well as in degenerative conditions such as Alzheimer's disease (Da Cruz, 2010) and semantic dementia (Hodges, Patterson, Oxbury, & Funnell, 1992; Kertesz, Jesso, Harciarek, Blair, & McMonagle, 2010; Snowden, Goulding, & Neary, 1989). For example, in the case of semantic dementia, the dissociation between preserved repetition and impaired semantic comprehension of the same words probably motivates the frequent questioning of word meaning by the patient ("Gorilla? … gorilla … what is gorilla?") (Kertesz et al., 2010). Questioning the meaning of words has been viewed as an important clue for the diagnosis of semantic dementia (Kertesz et al., 2010), and this verbal behaviour fits well with the characteristics of ME (Berthier, Dávila, & Torres-Prioris, 2016).

The paucity of reports on ME leaves important questions about its functional mechanism, neural basis and potential treatments unanswered. With the idea of gaining further knowledge on ME, the aims of the present study were: (a) to study ME in a person (CCR) with fluent aphasia and left temporo-parietal damage and interpret ME in the light of recent advances in the mechanisms underpinning language repetition and comprehension; (b) to report the effects of two separate treatment approaches (Constraint-Induced

Aphasia Therapy – CIAT, and memantine) on reducing detrimental ME in CCR; and (c) to examine the neural correlates of ME in CCR using multimodal neuroimaging.

ME in aphasia: to treat or not to treat?

Another unsettled question is whether or not ME in aphasia should be treated. Although different types of echolalia (automatic, mitigated) may be the only available overt language function in some patients (Hadano, Nakamura, & Hamanaka, 1998), there is little information on the possibility of exploiting echolalia to improve speech production, auditory comprehension or both (Kurland, Pulvermüller, Silva, Burke, & Andrianopoulos, 2012; Pulvermüller & Schönle, 1993). Pulvermüller and Schönle (1993) took advantage of the late emergence of verbal echoing (word and short phrases appeared 4 years after aphasia onset) to enhance speech production and comprehension skills in a formerly globally aphasic patient (KS) who otherwise had no efficient communication. Treatment of speech production deficits was implemented through speech acts named *requesting by selective repetition*, whereas to treat comprehension deficits KS was requested to pass a particular card to the examiner using sentences like "Please give me the rabbit?" or "Could I have the fork?". KS was treated in a dyadic setting using card games (an early version of CIAT – Pulvermüller et al., 2001) for 3 weeks (five sessions of 1 h per week), and a significant improvement of speech production and comprehension was found. In the same vein, Kurland et al. (2012) found that CIAT improved object naming in a patient with chronic transcortical motor aphasia who repeated several times his own successful naming productions in a "self-generated ritual" (a kind of ME) to further improve his performance. Therefore, this preliminary evidence suggests that incorporating verbal echoing in an intensive language-action therapy (CIAT) may be useful to improve speech production, naming and comprehension in cases with *nonfluent* speech.

The logical question now is which strategy should be adopted when ME occurs in cases of aphasia with *fluent* speech and variable deficits in auditory comprehension. Based on accounts of ME, which viewed it as a compensatory strategy aimed to improve meaning access in the auditory modality (Ford, 1989; Pick, 1924; Stengel, 1947), permitting the use of ME in aphasia therapy and real life seems to be a correct strategy. Nevertheless, there are no contemporary empirical studies that confirmed that this should always be the case. Note that ME has been observed in different types of aphasias, including some with preserved auditory comprehension, thus implying that the production of ME is not always to assist meaning access during comprehension. Note also that some patients with ME repeated the same stimulus several times (e.g., Examiner: "Show me your cheek"; Patient LL: "Cheek, cheek, cheek, cheek, cheek, cheek, cheek" – Kohn & Friedman, 1986, pp. 302–303), an incessant and repetitive behaviour that unfailingly interferes with everyday communication. Therefore, it remains to be determined under which circumstances the use of ME exerts a beneficial or detrimental role in language functions amongst patients with aphasia. Also, it should be taken into account that for the same patient performance in verbal repetition and echoing is not always consistent and may vary from one stimulus to other similar stimuli. An early case study of a patient with conduction aphasia demonstrates variability in verbal echoing-repetition, awareness of performance and voluntariness of echoing words (Brown, 1975) (see an excerpt of this case in[4]).

Since we noticed that ME in CCR interfered with functional communication, we evaluated the effect of two different interventions (CIAT and memantine) on reducing the interference of ME on communication. Below, we briefly describe the rationale for implementing each therapy. Stroke lesions induce synaptic modifications that interfere with neural plasticity, and it has been hypothesised that leveraging the amount of neurotransmitters with drugs may improve neural plasticity and recovery of cognitive deficits, including language (Berthier, 2014). It is well established that treatment with memantine attenuates language and communication deficits in patients with stroke, Alzheimer's disease and Parkinson's disease complicated with dementia (for a recent review, see Tocco et al., 2014). Memantine downregulates exaggerated glutamatergic activity associated with stroke, eventually reducing its toxic effects on brain tissue (Parsons, Stöffler, & Danysz, 2007). This favourable action of memantine may help to return brain activity to physiological levels, restoring normal learning mechanisms (see further data in Barbancho et al., 2015; Berthier et al., 2009). By virtue of its beneficial action on reestablishing physiological neural activity, memantine also primes brain structures to be more responsive to intensive aphasia therapy (e.g., CIAT), which in turn stimulates functional reorganisation of language networks in both cerebral hemispheres (Barbancho et al., 2015).

CIAT is an intensive language-action therapy for aphasia (for reviews see Difrancesco, Pulvermüller, & Mohr, 2012; Pulvermüller & Berthier, 2008). CIAT implements massed practice (30 h within 2 weeks; 3 h/day) in a small-group setting (2–3 persons and a therapist) to promote learning-dependent plasticity. CIAT stimulates communicative speech acts such as "making a request" or "planning an action" (naming) (Difrancesco et al., 2012). Therefore, the application of CIAT exploits the functional links between language and motor neural networks by embedding speech acts in communicative contexts and it also aims to reduce the deleterious effect of learned nonuse (avoiding speaking due to lack of success) of potentially useful strategies (Berthier & Pulvermüller, 2011). Guidance by constraining gestures that replace verbal production is also used. These "constraints" can also be extended to restrict the use of maladaptive forms of verbal communication. In the case of CCR, a strategy of discouraging the use of ME during naming and requesting embedded in CIAT games was implemented (Egorova, Pulvermüller, & Shtyrov, 2014; Pulvermüller & Berthier, 2008). Although CIAT is a group therapy, guidance for using correct communication can be individually tailored to the participant's needs (modelling and shaping constraints) (Difrancesco et al., 2012). Thus, one objective in the treatment of CCR was to evaluate whether discouraging the use of ME in speech acts (naming and requesting) was beneficial. Therefore, in the course of CIAT sessions, CCR was encouraged to remain silent during and briefly after receiving requests by other participants and then he was allowed to verbalise the response (McMorrow, Foxx, Faw, & Bittle, 1987). Note that although repetition of words and sentences is a skill usually potentiated in CIAT, in the case of CCR instructions to reduce ME were used. The decision to reduce ME by explicit instruction during therapy was based on clinical observation during baseline evaluation. It was observed that ME echolalia highly interfered within communication and made evaluations excessively long.

Neural correlates of ME

Aphasic patients displaying ME iteratively repeat words and phrase fragments that are difficult for them to understand (Pick, 1924). Although the neurobiology of ME is unknown, recent advances on the neuroimaging of normal and abnormal language may illuminate its neural mechanisms. Let us first consider the case of semantic dementia, a condition in which ME is remarkably frequent (Kertesz et al., 2010). In this circumstance, ME might result from compensatory activity of the left dorsal stream with the purpose of facilitating access to degraded semantic knowledge associated with left temporal lobe degeneration involving the ventral stream (e.g., uncinate fasciculus, inferior longitudinal fasciculus) (Agosta et al., 2013). In the same vein, one has to consider, in the second place, the fact that most reported cases of post-stroke aphasia showing instances of ME had fluent speech with impaired semantic comprehension at word and sentence levels and lesions primarily involving the left temporal lobe (Bormann & Weiller, 2012; Franklin et al., 1996; Hall & Riddoch, 1997). Therefore, following the valuable lessons provided by dual-stream models for speech comprehension (Hickok & Poeppel, 2015; Specht, 2013), ME would be interpreted as reflecting, a not always, successful plasticity-based mediation of repetition via an intact left dorsal stream in charge of auditory-motor integration when the left ventral stream, responsible for extracting meaning from words, sentences and narratives during auditory comprehension, is out of function (Berthier et al., 2016; Specht, 2013). Therefore, we hypothesise that ME in CCR resulted from activity of remnants of the left dorsal stream and the intact right dorsal stream aimed to compensate severe damage to the left ventral stream.

Case report

CCR was a 43-year-old right-handed man who was referred to our Research Unit of Cognitive Neurology and Aphasia for evaluation of fluent aphasia 15 months after suffering a haemorrhage in the left temporo-parietal region secondary to the rupture of vascular malformation irrigated by the choroidal artery. The haemorrhage was surgically evacuated uneventfully and some remains of the vascular malformation were treated later on with radiosurgery. CCR was discharged with a severe fluent aphasia with impaired comprehension and a right hemisensory loss. At the time of the initial language evaluation in our Unit (April 2003), his scores on the Western Aphasia Battery (WAB) (Kertesz, 1982) (spontaneous speech: 11, comprehension: 4.4, repetition: 4.2, naming: 4.5) indicated a moderately severe Wernicke's aphasia with marked ME.

Study design

In March 2005, CCR was recruited for participation in a randomised, double-blind, placebo-controlled, parallel-group study of both memantine and CIAT on chronic post-stroke aphasia (Berthier et al., 2009). Twenty-eight patients were included (14 memantine and 14 placebo) in the trial, and CCR was assigned to the placebo group. After baseline evaluation (week 0), CCR received placebo alone during 16 weeks, followed by a combined therapy with placebo and CIAT (weeks 16–18, 30 h of CIAT), placebo alone (weeks 18–20) and washout (weeks 20–24). Then, he was included in an open-label

extension phase of memantine (20 mg/day) without speech-language therapy (weeks 24–48). He was evaluated with the WAB at baseline and at weeks 16, 18, 20, 24 and 48. In this trial, patients were classified as "responders" to any intervention when they gained ≥5 points on the Aphasia Quotient (AQ) of the WAB (WAB-AQ) (this value exceeds the standard error of the test) (Berthier et al., 2009; Cherney, Erickson, & Small, 2010; Cherney et al., 2012). The study was registered with EudraCT (2004-002337-39), and the protocol for the study was filed with the open clinical trial registry (www.clinicaltrials.gov; Identification No. NCT00196703).

Baseline testing

In March 2005, language evaluation disclosed that all language deficits had improved (WAB: spontaneous speech: 15, comprehension: 7.0, repetition: 7.4, naming: 8.7). Spontaneous speech was fluent, grammatical and devoid of paraphasias, but mildly anomic. Despite these favourable changes, ME in spontaneous speech persisted unabated. In addition, on examination of auditory comprehension of the WAB, CCR had many occurrences of ME in all three tasks (Yes/No Questions, Auditory Word Recognition and Sequential Commands). Although according to the WAB taxonomic criteria the new aphasia profile was consistent with an anomic aphasia (Kertesz, 1982), the clinical pattern resembled a mild residual Wernicke's aphasia with prominent deficits at sentence level and features of word-meaning deafness (Bormann & Weiller, 2012; Bramwell, 1897; Kohn & Friedman, 1986). For example, when CCR failed to recognise auditory-presented words (body parts, objects, colours and proper names), he could rapidly recognise their meaning after reading them. Even in some occasions, when he missed the meaning of an auditory-presented word ("spoon") he wrote it with his index finger over the examining desk and after reading it he immediately recognised the word ("Oh! spoon").

Overall, language testing in CCR revealed impaired comprehension (auditory and written) and repetition at sentence level with preserved comprehension and repetition of single words. Auditory-verbal short-term memory was also impaired. Data on baseline testing is presented in Table 1. Language was assessed with several subtests of the Spanish version of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) (Kay, Lesser, & Coltheart, 1992; Valle & Cuetos, 1995), the Pyramids and Palm Trees Test (Howard & Patterson, 1992) and experimental tests evaluating repetition of words, nonwords and word lists (see methodology in Berthier et al., 2011, 2014). CCR had normal performance in several processing tasks tapping auditory phoneme discrimination (word and nonword minimal pairs and word minimal pairs requiring written selection), auditory (words) and visual (words and nonwords), lexical decision, and rhyme judgements. Comprehension of auditory and visual stimuli was average for words (spoken word-picture matching – PALPA 47, [.95]) except for finger recognition and right-left commands (auditory word recognition of the WAB: 55/60). Auditory and written sentence comprehension was moderately impaired (PALPA 55 and 56). Semantic processing was mildly impaired in picture naming but written naming, written spelling and oral reading of the same words (PALPA 53) were preserved. Auditory and visual synonym judgements (PALPA 49 and 50) and word semantic association (PALPA 51) were only impaired for low-imageability words. Performance on the Pyramids and Palm Tree Test was normal. Span for digits, words, nonwords and noun–verb sequences was markedly impaired. Table 2 shows baseline data

Table 1. Background language testing.[a]

Tests	CCR's scores (proportion)	Performance descriptor	Normative data[1]
Nonword minimal pairs (PALPA 1)			
Same (n = 28)	28 (1.0)	Normal	27.45 ± 0.99
Different (n = 28)	27 (.96)	Normal	27.09 ± 1.24
Word minimal pairs (PALPA 2)			
Same (n = 28)	28 (1.0)	Normal	27.54 ± 1.27
Different (n = 28)	28 (1.0)	Normal	27.68 ± 0.76
Word minimal pairs requiring written selection (n = 52) (PALPA 3)	52 (1.0)	Normal	51.45 ± 1.03
Auditory lexical decision: imageability × frequency (PALPA 5)			
High imageability–high frequency (n = 20)	19 (.95)	Normal	20.00 ± 0.00
High imageability–low frequency (n = 20)	20 (1.0)	Normal	20.00 ± 0.00
Low imageability–high frequency (n = 20)	20 (1.0)	Normal	19.95 ± 0.21
Low imageability–low frequency (n = 20)	19 (.95)	Normal	19.41 ± 1.15
Nonwords (n = 80)	70 (.87)	Impaired	78.18 ± 1.95
Visual lexical decision: imageability × frequency (PALPA 25)			
High imageability–high frequency (n = 20)	20 (1.0)	Normal	20.00 ± 0.00
High imageability–low frequency (n = 20)	20 (1.0)	Normal	19.95 ± 0.21
Low imageability–high frequency (n = 20)	20 (1.0)	Normal	19.77 ± 0.42
Low imageability–low frequency (n = 20)	19 (.95)	Normal	19.45 ± 0.99
Nonwords (n = 80)	77 (.96)	Normal	78.09 ± 2.79
Digit production (PALPA 13)	3	Impaired	5.91 ± 0.67
Matching span (PALPA 13)	4	Normal	6.18 ± 1.34
Word span[2]	2	Impaired	–
Nonword span[2]	1	Impaired	–
Pointing span for noun–verb sequences (PALPA 60)	2	Impaired	5.5 ± 1.59
Rhyme judgements × words (PALPA 15)			
Rhyme, same spelling (n = 15), different spelling (n = 5)	18 (.90)	Normal	17.41 ± 2.41
No rhyme (n = 20)	13 (.65)	Mildly impaired	17.64 ± 3.17
Spoken word–picture matching (n = 40) (PALPA 47)	38 (.95)	Normal	39.45 ± 1.67
Written word–picture matching (n = 40) (PALPA 48)	38 (.95)	Normal	39.64 ± 1.46
Auditory sentence comprehension (n = 60) (PALPA 55)	46 (.77)	Impaired	58.25 ± 2.61
Written sentence comprehension (n = 60) (PALPA 56)	48 (.80)	Impaired	57.73 ± 2.60
Picture and word semantics (PALPA 53)			
Picture naming (n = 40)	35 (.87)	Impaired	38.86 ± 1.82
Written naming (n = 40)	36 (.90)	Normal	38.18 ± 2.10
Repetition (n = 40)	40 (1.0)	Normal	40.00 ± 0.00
Oral reading (n = 40)	40 (1.0)	Normal	39.82 ± 0.83
Written spelling (n = 40)	39 (.97)	Normal	38.50 ± 1.88
Word semantic association (PALPA 51)			
High imageability (n = 15)	12 (.80)	Normal	13.41 ± 0.98
Low imageability (n = 15)	9 (.60)	Impaired	13.00 ± 1.73
Pyramids and Palm Tree Test			
Pictures/pictures (n = 52)	50 (.96)	Normal	–
Words/words (n = 52)	51 (.98)	Normal	–
Auditory synonym judgement (PALPA 49)			
High imageability (n = 30)	28 (.93)	Normal	29.64 ± 0.64
Low imageability (n = 30)	23 (.77)	Impaired	28.00 ± 2.41
Visual synonym judgement (PALPA 50)			
High imageability (n = 30)	30 (1.0)	Normal	29.73 ± 0.54
Low imageability (n = 30)	21 (.70)	Impaired	28.32 ± 2.49

[a]All tests are from PALPA unless specified; [1]Normative data from Valle and Cuetos (1995); [2]Experimental tests (unpublished); The labels "normal" and "impaired" in the column "performance descriptor" have been obtained by comparison with normative data.

on repetition testing. CCR repeated single words of different grammatical categories almost flawlessly (except for verbs), but nonword repetition was moderately impaired. Repetition of sentences (PALPA 12) and of different lists of two and three words was markedly impaired. In the course of sentence repetition tasks, CCR commented that he

Table 2. Background repetition tests.

Tests	CCR Score (proportion)	Performance descriptor	Normative data
Words, imageability × frequency (PALPA 9)			
High imageability–high frequency (n = 20)	20 (1.0)	Normal	20.00 ± 0.00[1]
High imageability–low frequency (n = 20)	20 (1.0)	Normal	19.82 ± 0.65
Low imageability–high frequency (n = 20)	20 (1.0)	Normal	19.68 ± 1.02
Low imageability–low frequency (n = 20)	19 (.95)	Normal	19.27 ± 1.93
Nonwords (n = 80)	59 (.74)	Impaired	77.68 ± 3.35
Words, grammatical class[2]			
Nouns (n = 60)	60 (1.0)	Normal	59.90 ± 0.26
Verbs (n = 50)	44 (.88)	Impaired	50.00 ± 0.00
Adjectives (n = 50)	49 (.98)	Normal	50.00 ± 0.00
Functors (n = 40)	39 (.97)	Normal	39.90 ± 0.26
Nonwords (n = 80)	60 (.75)	Impaired	78.70 ± 1.20
Repetition: Sentences (n = 36) (PALPA 12)	3 (.08)	Impaired	–
Word pairs[3]			
No delay direct (n = 55)	29 (.53)	Impaired	–
No delay inverted (n = 55)	30 (.54)	Impaired	–
Filled 5 sec. delay (n = 55)	14 (.25)	Impaired	–
Three word lists[2]			
High frequency			
Random word combination (n = 20)	1	Impaired	19.00 ± 0.8
Loosely constrained semantic information (n = 20)	0	Impaired	18.70 ± 1.0
Constrained semantic information (n = 20)	5	Impaired	19.40 ± 0.6
Low frequency			
Random word combination (n = 20)	0	Impaired	17.00 ± 2.5
Loosely constrained semantic information (n = 20)	0	Impaired	18.60 ± 1.3
Constrained semantic information (n = 20)	1	Impaired	18.70 ± 1.2

[1]PALPA's normative data from Valle and Cuetos (1995); [2]Normative data from Berthier (2001); [3]See description and normative data of repetition of word pairs and three-word lists in Berthier (2001) and Berthier et al. (2014). The labels "normal" and "impaired" in the column "performance descriptor" have been obtained by comparison with normative data.

tried to understand the meaning of each individual constituent word to keep on with the rest of the sentence. In other words, it seems that automatic repetition was not fully available to CCR, particularly for word lists or sentences. He also claimed that words in sentences were evanescent and rapidly disappeared from his memory.

ME in spontaneous speech

Methods

Instances of ME and allied phenomena (echo-answer, contamination) were registered during the exploration of spontaneous speech (information content) with the WAB, which assesses the levels of information conveyed by the patient in conversation (Kertesz, 1982). To elicit speech, CCR was asked six questions related to personal history, everyday activities, occupation and reasons for consultation. The responses to these questions were audiotaped and transcribed.

Results

CCR produced ME on several occasions (see transcription in the Appendix). In response to some questions (numbers 3 and 6), it was noticed that CCR continued repeating the same phrases just after answering the question correctly, thus implying that ME was not stopped after successful word meaning access. Fragmentation of the echolalic responses

(within- and between-words) (e.g., what-is-your-name) was observed in response to questions 3 and 5. Echo-answer was observed in response to question 4. There were no instances of other types of echolalia or contamination.

ME in comprehension tasks

Methods

Instances of ME were examined in several auditory comprehension subtests (Yes/No Questions, Auditory Word Recognition, and Sequential Commands) of the WAB.

Results and comments

Instances of ME were frequently heard in auditory comprehension tasks. CCR was aware of his auditory comprehension deficit, and he frequently asked for stimulus repetition to grasp its meaning. He continuously incorporated fragments or the complete question into his responses. On the Yes/No Questions subtest, CCR obtained a mildly impaired score (51/60 [.85]). However, the mildly impaired score was confounded by echolalic repetition of stimuli (12/20 [.60]) (see Table 3). Indeed, CCR echoed entire sentences (Examiner: "Are you a doctor?"; CCR: "Are you a doctor?.. I'm not a doctor!"), and he only rarely modified the content of the echoed sentence to make it more appropriate (Examiner: "Does it snow in July?"; CCR: "Does it snow in winter?"). In most instances, echoes were heard in syntactically complex constructions (Examiner: "Does March come before June?"; CCR: "come before?"). At times, when he had trouble understanding the meaning of a word ("chest"), he produced a phrase that contained the target word and repeated it several times to facilitate its comprehension (e.g., "my chest hurts, my chest hurts"). Testing of Auditory Word Recognition showed mildly impaired performance (55/60 [.92]), and this task elicited ME in 12 of the pictured objects (n = 60) and subvocal ME (lip movements without making audible sounds) was additionally produced in other five items. Instances of ME were heard in eight words that apparently did not entail difficulty in understanding (a correct response was given) and in four words that CCR did not comprehend (incorrect or no response given). ME mainly occurred with targets signalling body parts, fingers and right-left body parts (Examiner: "point to the right cheek"; CCR: "right cheek? … the right cheek? … what is the right cheek? … right cheek … I can't"). A plausible interpretation here is that ME was aiding comprehension and, thereby, for many words in which he produced ME he was able to give the correct response. Other interpretation could be that he had no comprehension difficulty for these particular items, but he repeated these words because of an inhibitory control deficit.

Testing the Sequential Commands subtest revealed a moderate impairment (34/80 [.42]) and CCR produced ME in 10 out of 11 commands. In some items, he asked the examiner to repeat the command arguing that he "missed" information. For example, the request to execute the command "point to the pen with the book" (item 5) elicited the echolalic response "point to, point to, point to the pen…. book" and then he could complete part of the requested action correctly. CCR was not disappointed by the frequent occurrence of ME, rather he insisted that it was the best way to understand word meaning. The fact that single words and simple sentences elicited much less echolalic responses than complex sentences probably reflects a compensatory mechanism to the increased difficulty in comprehension and memory load required by the task. This interpretation does not exclude the fact that an additional inhibitory control deficit could mediate ME.

Table 3. Presence of ME on individual responses to Yes/No Questions test at baseline, different time points during treatment, and after 10 years of ending drug treatment.

Western Aphasia Battery Auditory Verbal Comprehension: Yes/No Questions	Baseline Wk 0	Placebo Wk 16	Placebo & CIAT Wk 18	Placebo Wk 20	Washout Wk 24	Memantine Wk 48	Ten-year follow-up
1. Is your name Perez? ("no" should be correct)	∏	ME	ME	∏	ME	ME	ME
2. Is your name Garcia? ("no" should be correct)	ME	ME	ME	ME	ME	ME	ME
3. Is your name (*real name*)?	ME	∏	∏	∏	∏	∏	∏
4. Do you live in Barcelona? ("no" should be correct)	ME	∏	ME	∏	ME	ME	ME
5. Do you live (*real residence*)?	ME	∏	∏	∏	ME	∏	ME
6. Do you live in Madrid? ("no" should be correct)	ME	ME	∏	∏	∏	ME	∏
7. Are you a man/woman ("yes" should be correct)	ME	ME	∏	∏	ME	∏	∏
8. Are you a doctor? ("no" should be correct)	∏	∏	ME	∏	∏	∏	∏
9. Am I a man/woman ("yes" should be correct)	ME	∏	∏	∏	∏	∏	∏
10. Are the lights on in this room? ("yes" should be correct)	∏	∏	∏	∏	∏	∏	∏
11. Is the door closed? ("yes" should be correct)	ME	ME	∏	ME	ME	∏	ME
12. Is this a hotel? ("no" should be correct)	ME	ME	ME	∏	∏	∏	∏
13. Is this (*real test location*)?	∏	ME	∏	∏	∏	∏	∏
14. Are you wearing red pyjamas? ("no" should be correct)	ME	ME	∏	∏	ME	∏	ME
15. Will paper burn in fire?	∏	ME	∏	∏	∏	∏	ME
16. Does March come before June?	∏	∏	∏	∏	ME	∏	ME
17. Do you eat a banana before you peel it?	∏	∏	∏	∏	∏	∏	∏
18. Does it snow in July?	ME	∏	ME	∏	ME	∏	∏
19. Is a horse larger than a dog?	∏	∏	∏	∏	∏	∏	ME
20. Do you cut the grass with an axe?	ME	ME	∏	∏	∏	∏	ME
Instances of ME (%)	12 (60)	10 (50)	6 (30)*	2 (10)***	9 (45)	4 (20)**	10 (50)
Total Test Score (max: 60)	51	54	51	54	54	54	54
Western Aphasia Battery-Aphasia Quotient (max: 100)	76.2	74	78.2	78.6	79.6	82.2	83.0
Spontaneous speech (max: 10)	15	15	16	16	16	17	17
Auditory comprehension (max: 10)	7	6.7	7.7	7.3	7.9	7.2	7.1
Repetition (max: 10)	7.4	7.6	7.4	7.7	7.4	8.0	8.8
Naming (max: 10)	8.7	7.7	8.0	8.4	8.5	8.9	8.6

Endpoints were at weeks 16 and 18 (see further details in Berthier et al., 2009). ME indicates mitigated echolalia (see text for examples), ∏ absence of ME. *$p = 0.031$; **$p = 0.002$; ***$p = 0.008$ (all McNemar test, two-tailed).

ME: word repetition versus word definition

Methods

CCR was given a list of words for repeating and defining, similar to the one used by Franklin et al. (1996) in a patient with word-meaning deafness. In our case, stimuli ($n = 80$) were selected from the PALPA subtest 9 (Repetition: Imageability × Frequency). CCR heard each word, repeated it and then gave a verbal definition. The accuracy of word definition was independently analysed by two of us (MLB and MJT-P).

Table 4. Brain activation during word and nonword repetition.

	Anatomical area	Hemisphere	Cluster size (voxels)	Peak coordinate		
				x	*y*	*z*
Word > Rest	Precentral gyrus	R	1693	54	0	48
	Precentral gyrus	L	774	−48	0	52
	Inferior frontal gyrus	L	610	−46	22	14
	Supplementary motor area	L	313	−2	−2	60
	Inferior frontal gyrus	R	304	48	40	14
	Cerebellum	R	285	22	60	−20
	Cerebellum	L	222	−22	−62	−20
	Lingual gyrus	L	121	−6	−74	0
	Anterior cingulate cortex	R	70	4	26	36
	Cerebellum	L	58	−20	−66	−52
	Postcentral gyrus	R	40	64	−20	14
	Middle temporal gyrus	R	38	66	−34	0
	Lingual gyrus	L	35	−6	−78	−14
Nonword > Rest	Precentral gyrus	R	3944	54	0	48
	Middle temporal gyrus	L	2426	−46	0	54
	Supplementary motor area	R	1378	2	0	66
	Inferior parietal lobe	L	594	−40	−36	38
	Cerebellum	R	490	24	−60	20
	Inferior parietal lobe	R	407	48	−30	54
	Cerebellum	L	358	−22	−60	−22
	Cerebellum	R	79	14	−68	−52
	Cerebellum	L	79	−18	−66	−54

All peaks reported are significant at $p < 0.05$ (FWE corrected at cluster level), with 30 voxels spatial cluster extent.

The presence of ME in the word definition task was not considered for accuracy decision. Since CCR had fluent mildly anomic spontaneous speech, the definitions were scored using fairly lax criteria. For example, the question: "What is a bed sheet?" elicited a definition "it's part of the clothes for sleep … the bed … to cover the bed", which was judged as an adequate rendition of the word "bed sheet". Inter-rater agreement was high (.93), and the few instances of disagreement were solved by consensus.

Results and comments

Performance on word repetition was almost flawless (79/80 correct [.98]). However, definition of the same words after auditory presentation was markedly impaired (28/80 [.35]) ($p < 0.0001$, Fisher Exact Test, two-tailed). Results for the repetition test are shown in Table 2. There also was a strong effect of imageability on word definition (high imageability: 24/40; low imageability: 4/40; $p < 0.001$, Fisher Exact Test, two-tailed), but not on word frequency (high frequency: 13/40; low frequency: 15/40, $p = 0.815$). Further analysis of word definition revealed more instances of ME when CCR was impaired in defining a word (26/52 [.50] words) than in correct definitions (9/28 [.32] words) ($p = 0.0636$, Fisher Exact Test, one-tailed). The advantage for repetition relative to definition of the same words enlightens the easiness with which CCR repeated words that were otherwise difficult to define and understand, a dissociation already reported in another patient with ME (Bormann & Weiller, 2012). Moreover, the present data also indicates that difficult-to-define words tend to be associated with more instances of ME.

ME: sentence repetition versus sentence comprehension

Methods

Sentence repetition was assessed with the Repetition: Sentences subtest of the PALPA (test 12). CCR was asked to repeat auditory-presented sentences. This test is composed of 36 sentences of different lengths (ranging from five to nine words). It contains reversible (n = 20) and irreversible sentences (n = 16). The most frequent ones are seven-word (n = 18) and six-word sentences (n = 8). The same sentences (n = 36) were selected from the Auditory Sentence Comprehension subtest (test 55) of the same battery to test sentence comprehension. In this test, CCR was asked to match an auditory-presented sentence with one of three visually presented figures, the target one and two distractors. This last test was used to elicit ME and to compare this verbal behaviour with the ability to repeat the same sentences. The two tests were administered 2 weeks apart. Accuracy in each test was examined. Although differences in repetition in the PALPA 12 and ME in PALPA 55 were analysed in all sentences, serial position curves were generated for all six-word and seven-word sentences.

Results and comments

In the Repetition: Sentences subtest (PALPA 12), CCR could only repeat five sentences correctly (three reversible and two irreversible), one of which was a successful self-correction ("The girl is, the girl is … scaring …, no!! the girl is washing the dog"). Thus, he produced 31 incorrect repetitions. CCR tended to repeat the first two words of target sentences, omitting the last two words. Specifically, repetition of the first and second words in the analysis of seven-word sentences was flawless (both 18/18 [1.0]). Conversely, CCR repeated correctly only 3/18 (.17) of penultimate words and 2/18 (.11) of last words. Similar results were found for six-word sentences. He could successfully repeat 8/8 of first words and 8/8 of second words but he could only repeat 4/8 (.50) of penultimate words and 3/8 (.37) of last words. In both, seven and six word sentences, a marked decrease in number of word repeated was observed for the forth (middle) position words (Figure 1).

In the Auditory Sentence Comprehension subtest (PALPA 55), used to elicit ME, a different pattern was observed. CCR was able to correctly match with the corresponding figure 32/36 of the presented sentences. In this test, CCR produced ME in 24 out of 36 sentences (.67) and frequently asked for stimulus repetition. Further analysis of the most frequent sentences (seven and six words) disclosed that instances of ME were less frequent in the first and last words and more frequent in words in the middle of the sentence. In seven-word sentences, CCR had instances of ME in 3/18 (.17) of first words and in 5/18 (.28) of second words, but a peak of ME was observed in the middle of the sentences (fourth word) (10/18 [.55]). Instances of ME diminished in the last part of the sentences (penultimate words: 3/18 [.17]; last words: 0/18 [.00]). Similar findings were observed in six-word sentences; ME was less frequent in the initial part (first words: 2/8 [.25] second words: 3/8 [.37]) and the last part (penultimate words: 3/8 [.37]; last words: 3/8 [.37]) of the sentences. In both, seven and six word sentences, a pronounced increase in ME was observed in forth (middle) position words (Figure 1). These deficits (impaired repetition of the words from position 3 onwards with ME of words in position 4) may be attributed to reduced auditory-verbal short-term memory

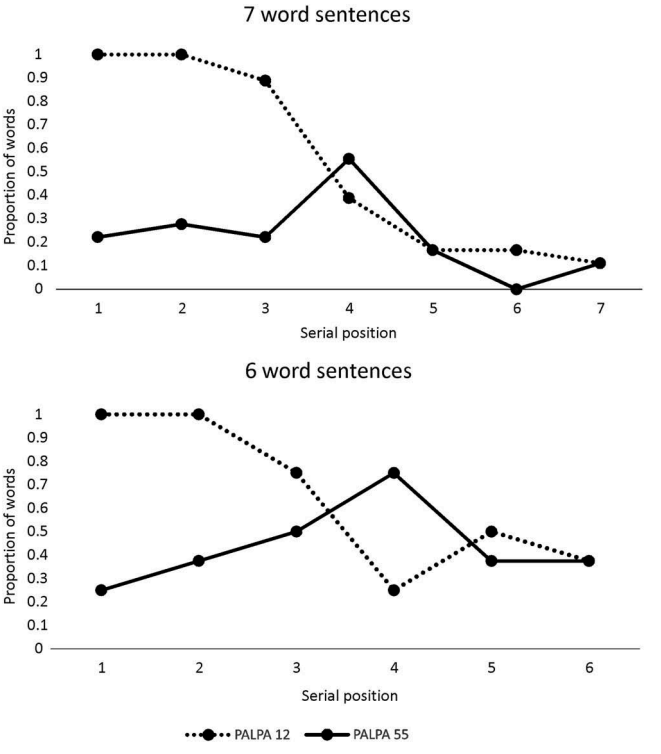

Figure 1. Serial position of words repeated during a sentence repetition task (dashed line) and instances of ME in an auditory sentence comprehension task (continuous line) subtests are represented. Points on the curves depict the proportion of words correctly repeated (PALPA 12) or echoed (PALPA 55) in each position of the sentences. Results are shown for all six-words and seven-words sentences that were common to both tests.

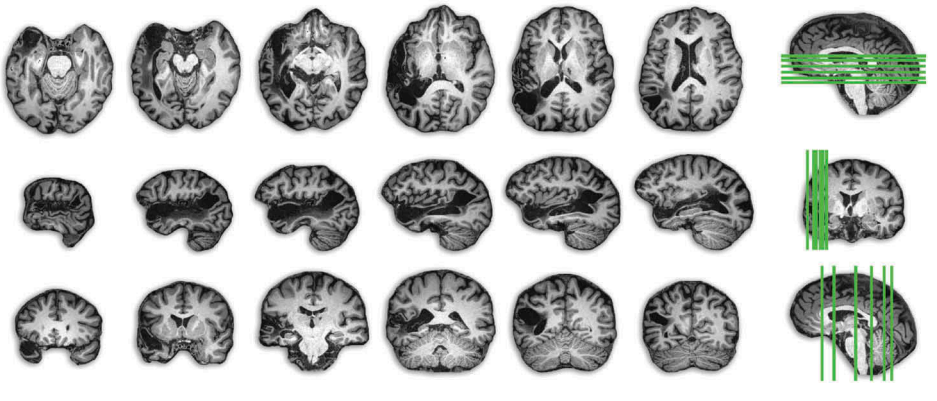

Figure 2. Depiction of the left-hemispheric structural lesion of CCR acquired in 2016. High-resolution (3-T) axial (top row), sagittal (middle row) and coronal (bottom row) MRI views in native space of T1-weighted image show a large left hemisphere lesion (see further details in text). Neurological convention is used. [To view this figure in colour, please see the online version of this journal.]

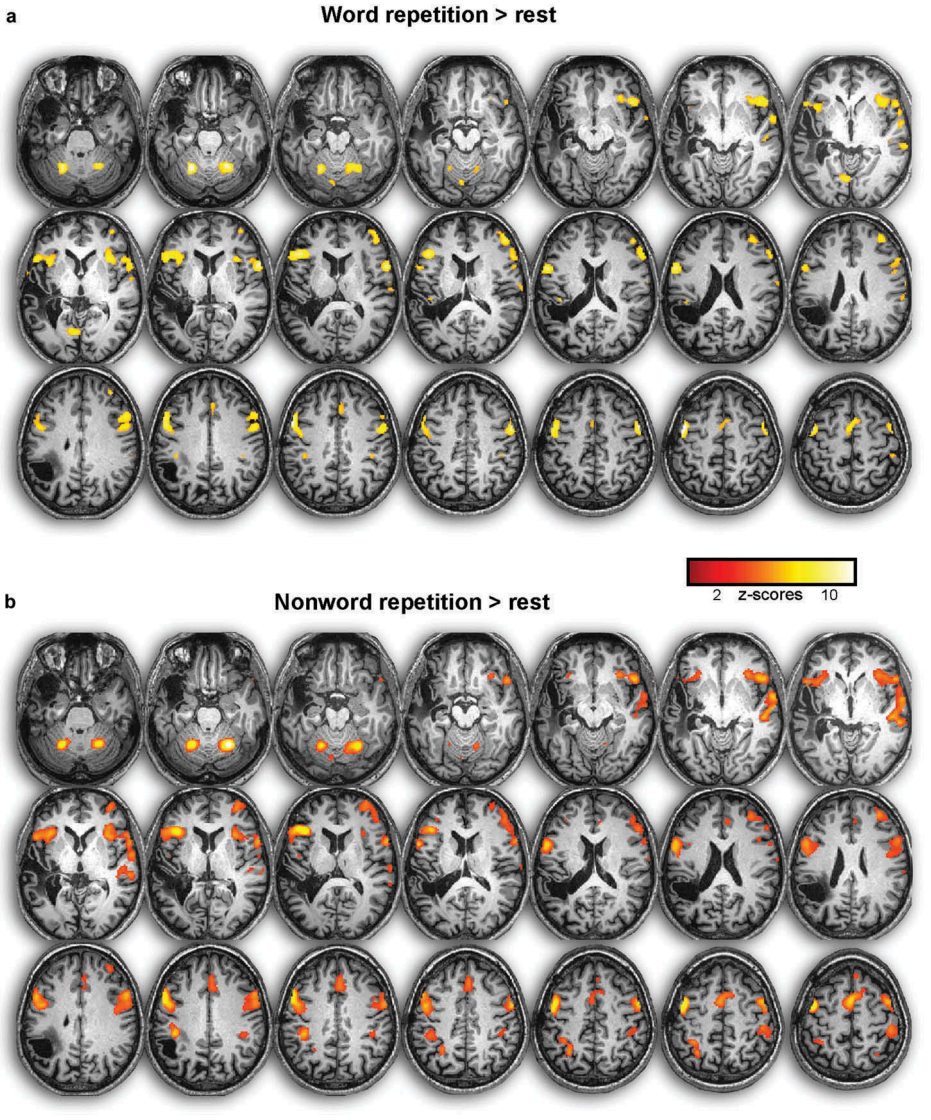

Figure 3. fMRI activations during covert repetition of words (a) and nonwords (b). Both contrasts show bilateral activations in the auditory-motor circuit, including the frontal, parietal and temporal areas related to language processing. Activations are also seen in the vermis and both cerebellar hemispheres. Also note that some small clusters of activations are localised in the left deep posterior temporal cortex that remains non-damaged. Axial views of the functional activation results are shown at $p < 0.05$ FWE-corrected threshold superimposed on the patient's T1 structural image in standard MNI space. Neurological convention is used. The activation in the inferior parietal cortex was larger in the nonword repetition condition, which fits well with the lexicalisation trend shown by the patient when he was required to repeat nonwords. [To view this figure in colour, please see the online version of this journal.]

(CCR had an auditory matching span of four items). It is possible that the maintenance of the verbal information during repetition was evanescent after words in positions 3 and 4 and that CCR produced ME to recover these words. Moreover, the role of an

unstable attentional control needed to support both word identity and word order for accurate comprehension of sentences (Majerus, 2013) might also be implicated.

Treatment

Methods

The effects of different interventions on the global severity of aphasia and ME were evaluated (see Study Design given earlier). The primary outcome measure of this trial was the AQ of the WAB for detecting beneficial changes in the global severity of aphasia. For the particular case of CCR, the number of instances of ME in the Yes/No Questions subtest of the Auditory Verbal Comprehension of the WAB was considered as a secondary outcome measure. The presence of ME was considered detrimental to CCR's communicative skills. Therefore, restrictions in the number of times that CCR asked for stimulus repetition and in the production of ME were introduced during CIAT (weeks 16–18), and the impact of these constraints was evaluated two after ending CIAT. The procedure for the restrictions of ME in the course of CIAT sessions was as follows: CCR was encouraged by the therapist to remain silent during and briefly after receiving requests by other participants and then he was allowed to verbalise the response. The time to complete a comprehension task and its score was used as a measure of response to treatment. The time to complete the task was only registered in the Auditory Sentence Comprehension test (PALPA 55). Attempts to restrict ME in the baseline evaluation (week 0) were unsuccessful due to CCR's inability to inhibit ME. Therefore, at the baseline evaluation, no restrictions were introduced. Restrictions were only applied during week 20 under two different conditions on two separate days. On the first day of evaluation, the stimulus sentences were presented once and only one instance of ME was allowed, whereas on the second day of evaluation stimulus sentences were again presented once, but this time no ME was permitted. The time to complete the tests and scores was registered in the three evaluations (Baseline, week 20 day 1 and week 20 day 2). Results of other secondary outcome measures (language and memory) at different endpoints are shown in a table in Supplementary information.

Results and comments

Results on the oral subtests of the WAB showed that CCR obtained modest benefits in aphasia severity (<5 points on the WAB-AQ) in evaluations at weeks 16, 18, 20 and 24, but he was considered a "responder" in the open-label extension phase under memantine treatment (week 48), and these gains in the global aphasia severity remained stable 10 years after ending this pharmacological phase. Despite the non-response to placebo alone and placebo combined with CIAT in aphasia severity, qualitative analyses of the Yes/No Questions subtest of the Auditory Verbal Comprehension (WAB) revealed significant decrements in comparison with baseline on ME after ending CIAT (week 18) ($p < 0.031$), 2 weeks later (week 20) ($p < 0.002$) and under memantine treatment (week 48) ($p < 0.008$). However, the long-term follow-up evaluation (10 years after ending the drug trial) revealed an increment in ME (Table 3).

Analysis of ME during auditory sentence comprehension without restrictions in the baseline evaluation (Week 0) revealed that most stimulus sentences (e.g., "The dog is approaching the girl") were repeated several times to CCR until he was ready to choose a response. The time to complete the test was 48 min, and his score was mildly impaired (52/60 [.87]). In two post-CIAT evaluations performed 2 weeks after ending CIAT (week 20), the time to complete the task was reduced to 21 min in both evaluations and CCR obtained similar scores (day 1: 46/60 [.77]; day 2: 45/60 [.75]), which were only slightly below the baseline score. These results suggest that constraints introduced within CIAT were useful to reduce requests of stimulus repetition and ME. A 6-month treatment with memantine alone (not associated to speech-language therapy) also significantly reduced the instances of ME during comprehension (baseline: 12/20 [.60] versus memantine: 4/20 [.20], $p < 0.002$, McNemar Test, two-tailed) and improved aphasia severity (baseline WAB-AQ: 76.2; memantine WAB-AQ: 82.2).

Follow-up evaluation

Methods

Ten years after ending the open-label extension phase of the memantine trial, CCR was contacted to undergo a long-term evaluation of language deficits including ME and also to examine the neural correlates of verbal repetition as well as the state of the resting state network and the language-related white matter pathways of ME using modern neuroimaging techniques.

Language testing

Methods

Language performance and ME were again assessed with the WAB (Kertesz, 1982). Further testing included repetition of words and nonwords (Repetition: Imageability × Frequency, PALPA 9) and digit production (PALPA 13).

Results

Evaluation of aphasia severity with the WAB revealed stable language performance (AQ = 83) compared with the previous evaluation under memantine treatment (AQ = 82.2, week 48). However, there was an increment in ME when it was assessed with the Auditory Verbal Comprehension: Yes/No Questions (see Table 3). Further testing revealed that repetition remained preserved for words (78/80 [.98]) and impaired for nonwords (58/80 [.73]), and that word span (Digit score = 3) was also impaired.

Neuroimaging

Structural MRI

The MRI shows an extensive lesion involving part of the temporal (anterior temporal pole, superior and middle temporal gyri) and the inferior parietal cortices (angular gyrus) in the left hemisphere (Figure 2). A small lacunar infarction is seen in the right medial thalamus, but the rest of the right hemisphere showed no structural lesions.

Functional MRI

Methods

Functional magnetic resonance imaging (fMRI) was used to study the activation pattern elicited during word and nonword repetition (*task-related fMRI*). In the task-related fMRI, the patient underwent two covert repetition activation tasks in two different runs. The word repetition task contained 40 high-frequency, concrete Spanish nouns [e.g., "casa" (house)], whereas the nonword-repetition task contained 40 nonwords that were derived from real words ["piedra" (stone) → *pierla*] by substituting the phonemes on the basis of Spanish phonotactical rules. For each task, four active blocks (including 10 items [words or nonwords]), each lasting 30 s, were presented alternating with four baseline-resting blocks of the same duration. Before the scanner session, performance on the word and nonword repetition tasks was evaluated. Then the patient underwent a resting state-fMRI (rs-fMRI) in order to retrieve the resting state networks. Finally, diffusion tensor imaging (DTI)-tractography was used to evaluate the integrity of the white matter pathways that might underlie ME. Deterministic tractography method was used to reconstruct white matter tracts. For further details about the fMRI, resting-fMRI and DTI acquisition, as well as the preprocessing and analysis, see Supplementary Information.

Results

fMRI activation during word and nonword repetition

The comparison of the blood-oxygen-level dependent (BOLD) response in the Word condition > rest yielded activations in the bilateral premotor cortex and the inferior frontal gyrus in the frontal cortex, the bilateral cerebellum and the right anterior middle temporal gyrus (Figure 3 and Table 4). A very similar pattern of activations was observed for the Nonword > rest comparison, except for the presence of activation in the inferior parietal cortex bilaterally (conditioned by the lesion in the left hemisphere) and for the fact that the clusters of activation were more extensive (Figure 3(b) and Table 4). The behavioural performance on both tasks outside the scanner showed that single word repetition was preserved (39/40) but nonword repetition was abnormal (29/40).

Resting state functional connectivity

A right-lateralised fronto-parietal network (Figure 4) was retrieved covering regions in the prefrontal cortex, the inferior parietal cortex and the superior temporal gyrus. Interestingly, although the classical left-lateralised fronto-parietal network (as reported, for example, in Beckmann, De Luca, Devlin, & Smith, 2005) was not found, a corresponding bilateral fronto-parietal network was retrieved (see Figure 4). This highlights the dynamic bilateral adaptation of the resting state networks when the damaged left fronto-parietal network is unable to support its corresponding language functions. Finally, the classical default mode network was also retrieved in CCR (Figure 5).

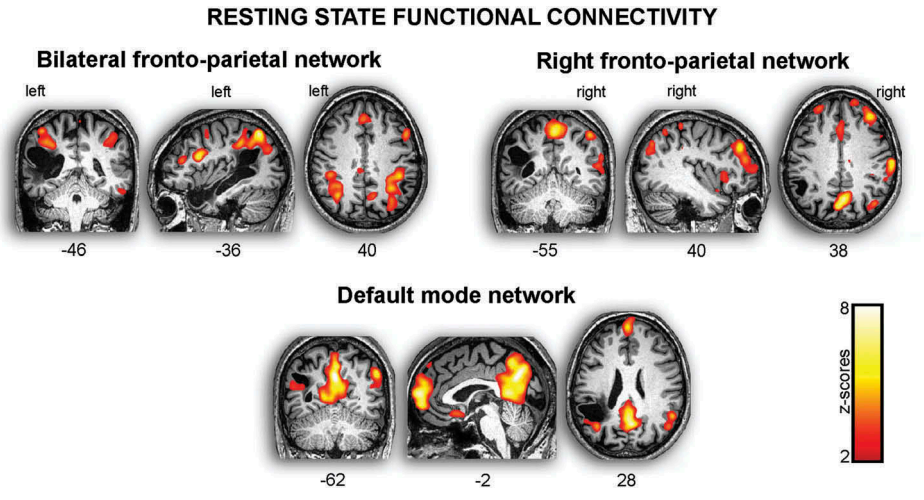

Figure 4. Resting state functional connectivity networks in patient CCR. Depiction of three classical resting state networks is shown. Note that in healthy subjects two lateralised fronto-parietal networks, mirroring each other, are normally found. The right fronto-parietal network was found in CCR, whereas the left fronto-parietal network shows lesion-induced functional plastic reorganisation resulting in a more bilateral pattern of coactivation (bilateral fronto-parietal network). The default mode network remains bilateral in spite of the lesion. Each network is rendered over the T1 image in standard MNI space with coordinates in millimetres shown at the bottom of each view. Results are shown at $p < 0.01$ uncorrected threshold. [To view this figure in color, please see the online version of this journal.]

DTI-tractography

CCR's ventral and dorsal white matter pathways were reconstructed in both hemispheres. First, the classical ventral (inferior frontal-occipital fasciculus – IFOF) and dorsal (three segments of the arcuate fasciculus [AF]) left hemisphere pathways were dissected; second additional pathways associated with language in the left hemisphere (frontal aslant tract [FAT], superior longitudinal fasciculus I [SLF I], uncinate fasciculus [UF], inferior longitudinal fasciculus [ILF]), as well as in the right hemisphere, were reconstructed (see Table 5). Figure 5 shows CCR's white matter pathways. Briefly, in the left hemisphere, the anterior fronto-parietal AF segment as well as the posterior parieto-temporal AF segment was identified. Neither the direct fronto-temporal AF segment, the IFOF, nor the UF could be reconstructed. Hence, although no direct connection between the frontal and the posterior temporal cortices was found, indirect connections were available, which might also contribute to the occurrence of ME. These fully dissected indirect connections included the SLF I, the ILF as well as the FAT in the left hemisphere. As expected, all targeted pathways in the right hemisphere could be dissected.

Discussion

In the present study we (a) reappraised the concept of ME in aphasia; (b) reported the beneficial effects of two separate treatment approaches (CIAT and memantine) to

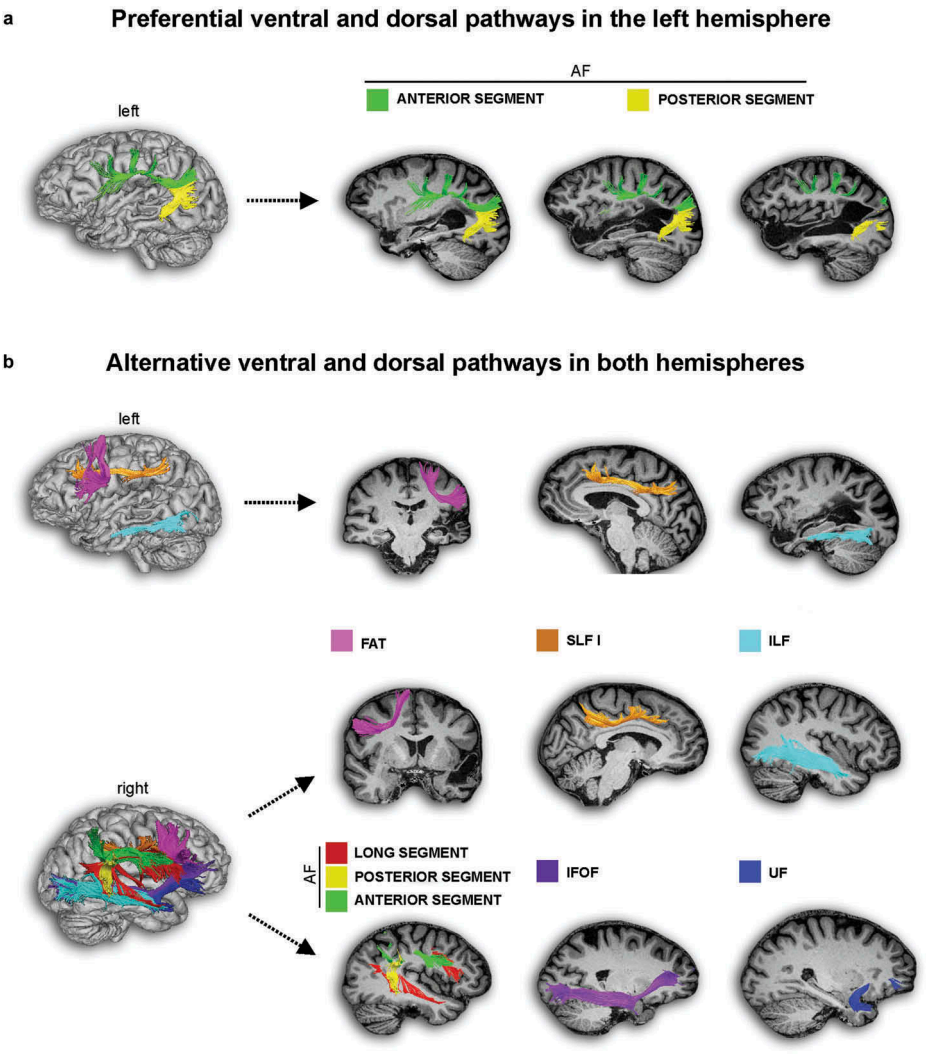

Figure 5. DTI-tractography reconstruction of the dorsal and ventral pathways in patient CCR. Panel A shows the remnant of the preferential pathways accounting for ME in CCR. Attempts to virtually dissect the three segments of the AF and the IFOF in the left hemisphere were made, but due to the lesion, neither the long AF segment nor the IFOF were found. Panel B shows the alternative pathways for the production of echolalia, which can aid in information transfer between language areas. While all the tracts were correctly reconstructed in the right hemisphere, no UF was found in the left hemisphere. Results are superimposed in the 3D rendering of the T1 patient's brain image (row 1), and into the T1 native image (rows 2–4). AF: arcuate fasciculus; SLF I: superior fronto-occipital fasciculus; FAT: frontal aslant tract; ILF: inferior longitudinal fasciculus; IFOF: inferior fronto-occipital fasciculus; UF: uncinated fasciculus. [To view this figure in color, please see the online version of this journal.]

reduce ME in CCR with fluent aphasia and left temporo-parietal damage; and (c) identified the neural basis of ME in CCR, which resulted from compensatory activity of remnants of the left dorsal stream and the intact right dorsal associated with severe damage to the left ventral stream.

Table 5. Fractional anisotropy (FA), volumes and lateralisation indices (LI) of the white matter pathways in both hemispheres.

	Number of streamlines		Tract volume			Mean FA	
Tract	RIGHT	LEFT	RIGHT	LEFT	LI[1]	RIGHT	LEFT
Arcuate fasciculus[2]	1393	630	18,320	8,293	0,377	0,425 ± 0,096	0,367 ± 0,084
Uncinate fasciculus	267	95	3,987	1,354	0,493	0,381 ± 0,086	0,312 ± 0,055
Inferior fronto-occipital fasciculus	369	251	9,586	3,069	0,515	0,449 ± 0,094	0,343 ± 0,077
Frontal aslant tract	297	175	5,335	4,704	0,063	0,392 ± 0,077	0,380 ± 0,083
Superior longitudinal fasciculus I	208	171	3,669	3,338	0,047	0,378 ± 0,075	0,426 ± 0,095
Inferior longitudinal fasciculus	774	204	11,166	2,456	0,639	0,447 ± 0,093	0,317 ± 0,076

[1]LI: lateralisation index calculated as: (Right vol − Left vol)/(Right vol + Left vol). A negative index indicates a left-side lateralisation; a positive index indicates a right-side lateralisation; an index of 0 means no lateralisation.
[2]In this table, the arcuate fasciculus has been computed as a whole.

Language features and functional mechanisms

ME is a common, but usually overlooked, symptom of aphasia (Berthier et al., 2016). Therefore, its functional mechanisms, neural basis, and treatment are still unknown. Here, we have described the case of CCR, a stroke patient with chronic fluent aphasia and prominent ME. At baseline evaluation (March 2005), he had a chronic fluent aphasia characterised by mild word-finding difficulties in spontaneous speech and severe impairments in comprehension and repetition of sentences, whereas single-word comprehension and repetition were relatively preserved. Repetition of nonwords and word lists of different lengths was impaired. Span tasks were also severely abnormal, but matching span for digits was mildly impaired. His performance on several tests of semantic knowledge was within the normal range. Thus, language deficits in CCR suggested a mild residual Wernicke's aphasia.

The most noticeable symptom in CCR was echolalic behaviour in the form of ME. He produced echoes in several contexts (spontaneous speech, word definition and different auditory comprehension tasks) (Appendix). For example, instances of ME were very frequent when CCR's ability to both define words and understand their meaning was impaired, thus reinforcing the proposed link between semantic deficits (production and comprehension) and ME. The production of ME allowed a successful meaning access for most words except for a few ones (body parts) in which it did not help comprehension, probably reflecting a degradation of semantic representations (Patterson et al., 2015). Up to now, the only explanation proposed in the literature to account for ME implicates impaired meaning access. Nevertheless, the picture is somewhat more complicated, in that CCR produced ME in words that entailed no difficulties in definition or understanding. This finding lends credence to the notion that complementary explanations are needed to understand the functional basis of ME. Based on our own data from CCR, two potential explanations can be suggested. One candidate explanation is based on a deficit in auditory-verbal short-term memory. We found more occurrences of ME in tasks composed of sentences than of single words, probably because repetition and auditory comprehension were more affected for sentences than for single words and also because auditory-verbal short-term memory was impaired. Analysis of repetition (PALPA test 12) and comprehension of the same semantically reversible and irreversible sentences (taken from PALPA test 55) provides some clues for linking ME with reduced

short-term memory in CCR. Analysis of serial position curves of the same six-word and seven-word sentences on these two tasks revealed that repetition was more accurate for the first and second words and that most instances of ME were heard during sentence comprehension in words of the medial part of sentences. These deficits most likely resulted from reduced auditory-verbal short-term memory required for the maintenance of the verbal information during repetition although an unstable attentional control needed to support both word identity and word order for accurate comprehension of sentences (Majerus, 2013) could also contribute to ME. Damage encroaching upon the left posterior temporal and inferior parietal cortices in CCR could account for deficits in sentence repetition (Selnes, Knopman, Niccum, & Rubens, 1985), comprehension of spoken sentences (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004) and auditory short-term memory for long word sequences (Leff et al., 2009; Salis, 2012). Under these adverse circumstances, ME has emerged in CCR to maintain active information when the short-term memory load is high (long sentences, semantically reversible sentences).

The other explanation which might account for ME is linked with a failure in response inhibition. We suggest that incompetent inhibitory control mechanisms may also justify repeating in a seemingly deliberate way the same word a number of times in previous cases of ME (e.g., seven times in Patient LL! – Kohn & Friedman, 1986, pp. 302–303) as well as in CCR. In general, it seems that these patients do not have appropriate inhibitory resources to stop repeating themselves many times although the incessant repetition does not facilitate accessing word meaning. Admittedly, this behaviour may reflect earnest efforts to access word meaning, but if these patients are requested to use short responses and asked not to repeat the content of questions, they often refrain from doing it (Lebrun et al., 1971). Also, note that early accounts viewed echolalia as a "release" symptom (Pick, 1924) and recent interpretations suggest that large lesions in the temporal lobe, like the one found in CCR, remove inhibitory influences over the perisylvian cortex (left inferior frontal gyrus) responsible for word and sentence repetition (Berthier, Pulvermüller, Green, & Higueras, 2006; Restle, Murakami, & Ziemann, 2012), thus favouring inefficient monitoring of automatic responses. In support, recent descriptions of ME in stroke aphasia emphasised the involuntary and out-of-control nature of ME even though the patients were aware of their own echolalia and unsuccessfully tried to control it (Hadano et al., 1998). In any case, further studies are warranted to establish the boundaries between automatic and voluntary repetition in ME.

Treatment approaches

Improvements promoted by the interventions were found in spontaneous speech, repetition and AQ of the WAB after prolonged treatment with memantine (weeks 24–48) but not in other endpoints. Evaluations just after ending 2 weeks of CIAT (week 18), 2 weeks later (week 20) and under memantine (week 48) additionally disclosed significant reductions of ME on an auditory comprehension test (Yes/No Questions of the WAB), producing no changes in the total scores of this task (range: 51–54 out of 60). Our positive results should be interpreted in light of some methodological issues. First, it could be argued that attenuation of ME at these endpoints merely reflect a general trend of improvement over time, and this possibility cannot be completely discarded. Note, however, that improvement of ME was not random as it did not occur at the end of the placebo (week

16) and washout (week 24) phases. Second, we need to consider that further improvement in ME 2 weeks after ending CIAT (week 20, two instances of ME) in comparison with CIAT (week 18: six instances of ME) may have resulted from the potential influence of test–retest. However, consider that lasting improvements in language functions in patients with chronic aphasia treated with CIAT have been reported (Meinzer, Djundja, Barthel, Elbert, & Rockstroh, 2005). Other potential confounds induced by repeated testing (e.g., increased familiarity with difficult words, decreased anxiety) need to be addressed in future cases. Despite these caveats, we suggest that the stable high performance (~.90) on the sentence comprehension task (Yes/No Questions subtest of the WAB) throughout the whole trial does not mean that CIAT and memantine were useless. Two evaluations of auditory comprehension of sentences restricting the use of ME revealed marked decreases in the time needed by CCR to complete the Auditory Sentence Comprehension subtest (PALPA 55) without causing important decrements in scores in both testing sessions relative to baseline evaluations where restrictions to ME could not be applied. Focusing attention on inhibiting verbal responses may have also played a role in reducing ME. Note that in the course of CIAT sessions CCR was encouraged to remain silent during and briefly after the auditory presentation of questions by other participants and then he was allowed to verbalise the response. Verbal instructions made by the therapist with the aim of attenuating imitative tendencies (see Bardi, Bundt, Notebaert, & Brass, 2015) could have contributed to decrease ME (McMorrow et al., 1987). In the same vein, a significant reduction of ME was also seen under memantine treatment. The likely mechanism for ME reduction promoted by this cognitive enhancing drug might be analogous to that induced by CIAT alone, that is functional reorganisation and strengthening of language circuits in both cerebral hemispheres (Barbancho et al., 2015; Mohr et al., 2016).[3]

Neural mechanisms

Multimodal neuroimaging in the current study provided us the opportunity to explore the anatomical and functional correlates of verbal repetition, providing some clues, albeit indirect, for understanding ME. Neuroimaging was carried out 10 years after ending the pharmacological treatment when the frequency of ME had returned to baseline levels. Our hypothesis that ME resulted from activity of remnants of the left dorsal stream and the intact right dorsal stream aimed to compensate severe damage to the left ventral stream has been confirmed. The fMRI study in CCR showed that there were no auditory inputs to the left temporal lobe during auditory repetition of words and nonwords, but there was a significant activation of the right primary auditory cortex, right superior temporal gyrus and dorsolateral prefrontal region bilaterally. This suggests that auditory comprehension relied on the compensatory activity of the right hemisphere (Berthier, Lambon Ralph, Pujol, & Green, 2012; Musso et al., 1999). Since the presence of ME entails the correct repetition of words that are usually poorly understood (Berthier et al., 2016; Pick, 1924), the bilateral pattern of activation after a large lesion in the left hemisphere highlights the involvement of both the perilesional sites (inferior frontal gyrus and dorsolateral frontal cortex) and their homotopic counterparts in the right hemisphere, reflecting the participation of remnants of the left and fully developed right dorsal streams in ME. The functional reorganisation of the language system in CCR was also supported by the resting state analysis. Hence, while we have retrieved the default mode network (which is bilateral in healthy subjects) and the right-lateralised fronto-parietal network very similar to the ones

found in the healthy population (see Figure 5), we were not able to find the left fronto-parietal network (which is normally a mirror image of the right-lateralised one Beckmann et al., 2005; Smith et al., 2009). Instead, we found a bilateral fronto-parietal network which indicated that the intrinsic connectivity of the language-related brain areas in the left hemisphere during rest has recruited regions of the right hemisphere. Finally, analysis of DTI-tractography showed the absence of the ventral pathway in the left hemisphere (neither IFOF nor UF could be reconstructed), probably accounting for the deficits in auditory comprehension of CCR and the frequent instances of ME. Even though we were not able to find a direct AF segment, we reconstructed the anterior and posterior AF paths. Since we were unable to find the left direct AF segment, a pathway proposed to mediate word repetition (Saur et al., 2008), we assumed that the preserved indirect connection between the posterior temporal and the frontal cortex can explain the preservation of single-word repetition and ME as well as the limited ability to repeat more complex verbal stimuli (nonwords, word lists and sentences). Moreover, the role played by alternative preserved pathways in the left hemisphere in both ME and recovery of other functions is worth considering. Hence, in our patient, the required crosstalk between posterior and anterior regions may be assisted dorsally by the superior longitudinal fasciculus I. Thanks to the short U-shaped fibres and the frontal aslant tract, the information carried by the superior longitudinal fasciculus I can indirectly reach Broca's territory. Finally, fitting the functional results suggesting an important role of the right hemisphere activation in aphasia recovery (Hamilton, Chrysikou, & Coslett, 2011), we were able to reconstruct all the tracts in the right hemisphere, including the dorsal and the ventral classic pathways. Further studies are required to deeply explore the role of the right hemisphere in recovery as well as the functional reorganisation that might take place in the affected hemisphere through alternative pathways.

Further studies are needed to explore the frequency and characteristics of ME not only in samples of stroke patients, but also in other conditions (e.g., semantic dementia, Alzheimer's disease, herpes virus encephalitis) in which it is probably more prevalent. The functional mechanisms underlying ME and the role of interindividual variability on the clinical pattern need to be explored to inform therapists under which circumstances ME reinforces language comprehension or, as occurred in CCR, interferes with functional communication and rehabilitation.

Notes

1. The term echophenomena, also known as imitation behaviour (De Renzi, Cavalleri, & Facchini, 1996) or resonance behaviour (Rizzolatti, Fadiga, Fogassi, & Gallese, 1999), refers to an act of social dependence (person-based activation) characterised by a tendency to imitate the gestures and utterances that the examiner makes in front of the patient even when no specific instruction has been given to do so (Berthier, 1999; Ford, 1989; Stengel, 1947).
2. Word-meaning deafness is an exceptional disorder in which the patient "can repeat the words he heard without understanding their meaning" (Symonds, 1953, p. 3). The deficit in auditory comprehension is secondary to a dissociation between accurate phonological and semantic information (Bormann & Weiller, 2012; Kohn & Friedman, 1986). Auditory comprehension is abnormal, but comprehension of written and picture stimuli is normal. Word-meaning deafness usually occurs in cases of transcortical sensory aphasia, Wernicke's aphasia and conduction aphasia of mild severity.
3. Echo-answer refers to the superfluous incorporation of words from the question in the response, whereas contamination is the inadvertent inclusion of a word just heard into the

patient's response instead of the one he/she wanted to say (Lebrun et al., 1971). These phenomena often coexist with ME.

4. Four major types of repetition performance were observed. At times, single words were echoed correctly, apparently without awareness of the reiterated item for the followed continued and usually unsuccessful attempts to reproduce the echoed word. At other times, a word was repeated correctly with uncertainty or surprise on the performance. More commonly, repetition showed phonemic paraphasia. Verbal paraphasia was rarely observed. Finally, repetition occasionally was characterized by complete failure. These four responses ranged from the most automatic to 'the most "voluntary"' (Brown, 1975, p. 39).

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No potential conflict of interest was reported by the authors.

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Appendix

Transcription of Spontaneous Speech

Baseline Evaluation (01/04/05)

1. ¿Cómo está usted hoy?
-*Yo estoy* ahora mismo muy bien. Lo que pasa es que quiero saber muchas cosas. No sé si le habré explicado. Algunas veces estoy hablando y no entiendo.

1. How are you today?
– *Today*, I'm very well right now. What happens is that I want to know many things. I don't know if I have explained it already. Sometimes I'm talking and I don't understand.

2. ¿Vino antes aquí?
– ¿Perdón…? (el evaluador repite la pregunta). No, es la primera vez. En otro sitio sí. Me parece que será callarme y ver la palabra que me está diciendo usted, y ya está.

2. Have you been here before?
– Pardon? (examiner repeats the question). No, this is the first time. Somewhere else, yes. I guess I would be quiet and see the word you are telling me, that's all.

3. ¿Cómo te llamas?
– *¿Cómo-te-llamas?*… ya empezamos explicando… *¿cómo te llamas? ¿cómo me llamo?*… *me llamo*… *¿cómo me llamo?* (el paciente dice su nombre)… *¿cómo te lla-mas? me llamo* (el paciente dice su nombre) mi nombre… *¿cómo me llamo?*.

3. What is your name?
– *What-is-your name?* … here we start explaining … *what's your name?* … *what's my name?* … *my name* … *what's my name?* (the patient gives his name) … *what's your na-me?* my name is … (the patient gives his name) my name … *what's my name?*.

4. Dígame tu dirección
– *¿Mi dirección?*… No lo sé exactamente. En Alhaurín de la Torre… ya está todo dicho… Alhaurín de la Torre… la calle tal… el número tal

4. What is your address?
– *My address?*… I don't know exactly. In Alhaurín de la Torre… that street… that number.

5. ¿En qué trabaja?
– *¿En-qué-trabajas? Trabajaba* como funcionario de… en Alhaurín de la Torre…. número tal… bueno también lo sé… sí lo entiende. No sé.

5. Where did you work?
Where did you work? I worked as official of … in Alhaurín de la Torre … that number … well I also know it … yes understand. I don't know.

6. Cuénteme un poco por qué vino, ¿qué te ha pasado en tu cabeza?
– *¿Lo que me ha pasado? Lo que me ha pasado*… puf… *lo que me ha pasado*… fue la hemorragia cerebral. *¿Cómo me ha pasado?* Pues, le sé explicar todo, bueno todo lo que sé claro, evidentemente no soy médico (evaluador: sí, ¿qué pasó?)… Sí, *lo que me ha pasado*. Pues se lo diré. Estaba yo… bañando mmm… se estaba… estábamos bañando con hijo pequeño…me ha pasado a dolerme la cabeza. Fui al hospital del… en el hospital me han… me han… me han… bueno… encam… me han… cambiado…. bueno el verbo no sé, pero bueno (se atasca y el evaluador

pregunta "¿qué..?") que lo sé y me gusta explicar con tranquilidad.

6. Tell me a little about why you are here?, what happened in your head?
What happened? What happened … puff … *what happened* was … a cerebral haemorrhage. *How did it happen to me?* Well, I know how to explain you everything, well everything I know of course, obviously I'm not a doctor. (examiner: Yes, what happened?) … Yes, *what happened*. Well, I will tell you. I was … bathing … mmm … it was … we were … bathing with baby son … it happened started to have headache. I went to the hospital of … in the hospital they have … they have … they have … well … entered … they have changed … well I don't know the verb but well (the patient got stuck and the examiner: what?) that I know it and I'll like to explain it calmly.

Note: Instances of ME are shown in italics. Hyphenation is used to signal fragmented speech.