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An electrophysiological investigation of construction processing in the healthy, aphasic, and modelled human brain

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This work is dedicated to my parents; with it I'm saying thank you to them.

Abstract

Language sets humans apart from other animals. The human brain can learn and store a vast number of arbitrary meaningful symbols and combine them into a virtually infinite number of possible sequences. Recent neurophysiological research on language processing offers new insights into biological mechanisms underpinning storage and combination in the brain and recent linguistic approaches, like construction grammar, assume that language is the result of human cognitive abilities. Joining the two approaches, the neuroscientific and the constructionist one, may contribute to a better understanding of human language. On this basis, the present work addresses processing of constructions, defined as form-meaning pairs of varying degrees of complexity, including beyond single-word level, by way of electrophysiological methods and techniques (electroencephalography, EEG; Event related potentials, ERPs; time-frequency analysis of oscillatory brain activity). The neurobiological background is the cell assembly theory of language, which provides an explanation at the cellular level for electrophysiological evidence on language processing and is consistent with the emergence of constructions in the brain as a result of cognitive principles underpinning language. Assuming that linguistic information is stored and combined in the brain in form of groups of neurons bound together by links of different strength leads to some key predictions. The first is that retrieval of stored information and combination thereof must occur from the very beginning of language understanding in a parallel and highly integrated fashion. The second is that changes in construction processing in the brain as indexed by electrophysiological methods, i.e. ERPs, must be evident in case of cell assembly consolidation, like, for instance, during effective treatment of patients suffering from post stroke aphasia. The third is that brain patterns of activity which reflect language processing in the human brain must be replicated in biologically realistic computational models of language networks implementing the same biological principles that allow for cell assembly formation, and thus possibly for the emergence of constructions as well. These predictions were tested here in three different studies.

In the first study, ERPs were recorded from healthy subjects presented with two-word constructions that were either 1) well-formed; 2) “unstored”, if they contained a pseudo-

morpheme, thus appearing partly senseless like “jabberwocky” speech; 3) “ill-combined”, if violated subject-verb agreement rules; or 4) double violations, if they included both types of errors. The mismatch negativity (MMN), an early automatic language-related ERP component, showed interactions of storage-related and combinatorial deviance by 70 to 210 ms after the onset of the phrase-final syllable that disambiguated the strings. These results support early, simultaneous, and interactive retrieval and combination of linguistic information in construction processing, the matching the first of the three predictions formulated above.

In the second study, MMN responses to two-word constructions were recorded before and after intensive language therapy in patients with chronic post stroke aphasia (PSA). Constructions were in this case either well-formed and meaningful, or ill-combined, if they violated pronoun-verb agreement, or ‘jabberwocky’ constructions, if they included an unstored pseudoword. Clinical language testing with the Aachen Aphasia Test (AAT) showed behavioural improvement of the language function, which was accompanied neurophysiologically by enhanced MMN responses. MMNs to combinatorially correct and stored-item-containing mini-constructions and to “jabberwocky” sentences significantly increased after therapy. In contrast, no therapy-related changes in MMN responses to ill-combined constructions violating agreement were found. The MMN increases can be explained with neuroplastic changes related to consolidation of the cell assembly representations of constructions, also for ‘jabberwocky’ sentences, whose combinatorial structure was intact. These results indicate the restitution of construction processing in the brain by way of cell assembly consolidation thanks to therapeutic approaches driven by neurobiological principles of functioning of the human cortex. They also indicate, together with pre-existing evidence, that combinatorial mechanisms underlying morphosyntax are more resistant to neurorehabilitation efforts.

In the third study, data from a neural-network architecture that replicated physiological (i.e. associative hebbian and anti-hebbian learning) and anatomical (i.e. connectivity) features of primary, secondary and associative frontal, temporal, and occipital areas of the human cortex were analysed with Morlet wavelet time-frequency analysis. The instances of the network were previously successfully trained for simulating learning of simple constructions and the responses to the presentation of learned and novel, unfamiliar items were subsequently compared. The results revealed stronger high-frequency spectral power for the learned constructions, closely reflecting electrophysiological results from human studies. For the first time high-frequency oscillatory phenomena which index construction processing emerged in a biologically realistic, neurocomputational model of the cortical areas known to be relevant for language. The main findings (i) that the behaviour of the neuronal network, and, in particular, its patterns of oscillations emerging to stimulus words, replicated earlier experimental results and (ii) the observed patterns of oscillations in the network were mechanistically related to the action of distributed cell assemblies, provide strong support for the cell assembly theory of language.

Taken together, the results of the three different studies presented here draw a coherent picture joining constructionist approaches with neuroscientific evidence on language processing and indicate that constructions are grounded in the brain in form of cell assemblies that arise thanks to storage-related and combinatorial mechanisms, which appear to serve fundamental and distinct functions.

Zusammenfassung

Sprache unterscheidet den Mensch von anderen Tieren. Das menschliche Gehirn kann eine große Menge willkürlicher sinnvoller Symbole erlernen, speichern und zu einer nahezu unbegrenzten Anzahl möglicher Sequenzen kombinieren. Elektrophysiologische Forschung zur Sprachverarbeitung liefert neue Einblicke in die biologischen Mechanismen, die Speicherung und Kombination sprachlicher Inhalte unterstützen. Zugleich beruhen moderne linguistische Ansätze – wie etwa die *Construction Grammar* (Konstruktionsgrammatik) – auf der Annahme, Sprache sei das Ergebnis menschlicher kognitiver Fähigkeiten. Die Integration dieser neurowissenschaftlichen und konstruktivistischen Ansätze kann dazu beitragen, ein besseres Verständnis der menschlichen Sprache zu entwickeln. Die vorliegende Arbeit befasst sich mittels elektrophysiologischer Methoden (Elektroenzephalographie, EEG; ereigniskorrelierte Potentiale, EKP; Zeit-Frequenz-Analyse der oszillatorischen Hirnaktivität) mit der neuronalen Verarbeitung von Konstruktionen, die als Paare von Form und Bedeutung verschiedener Komplexitätsgrade auch über die Einzelwortebene definiert sind. Der neurobiologische Hintergrund ist die sogenannte *Cell-Assembly*-Theorie, die eine Erklärung auf zellulärer Ebene für elektrophysiologische Evidenz zur Sprachverarbeitung anbietet. Die Theorie ist darüber hinaus auch konsistent mit der Entstehung von Konstruktionen aus kognitiven Grundsätzen, die Sprache ermöglichen. Unter der Annahme, dass linguistische Informationen gespeichert und kombiniert werden durch Gruppen von Neuronen, die wiederum durch Verbindungen unterschiedlicher Stärke miteinander im Austausch sind, führt dies zu drei wesentlichen Vorhersagen. *Erstens*: Der Abruf gespeicherter Informationen und ihre Kombination aus dem Beginn des Sprachverstehens müssen parallel und hochintegriert erfolgen. *Zweitens*: Änderungen in der Konstruktionsverarbeitung, die sich in Ergebnissen elektrophysiologischer Untersuchungen wie EKPs widerspiegeln, müssen mit einer Konsolidierung der Zellzusammensetzung einhergehen, so etwa bei der wirksamen Behandlung von Patienten mit Aphasie nach einem Schlaganfall. *Drittens*: Muster neuronaler Aktivität, die der Sprachverarbeitung im menschlichen Gehirn zugrunde liegen, müssen in biologisch-realistisch Computermodellen von Sprachnetzwerken repliziert werden können; dabei werden die gleichen biologischen Prinzipien implementiert, die eine Bildung von Zellverbänden und damit

gegebenenfalls auch die Entstehung von Konstruktionen ermöglichen. Diese Vorhersagen wurden in drei verschiedenen Studien getestet.

In der *ersten* Studie wurden EKPs gesunder Probanden auf der Grundlage von Zweiwortkonstruktionen untersucht; diese waren entweder (1) richtig gebildet, (2) „ungespeichert“, wenn ein Pseudomorphem enthalten war, (3) „falsch kombiniert“, wenn die Subjekt-Verb-Kongruenz verletzt wurde, oder (4) „doppelt inkonsistent“, wenn beide Arten von Fehlern vorlagen. Die *Mismatch Negativity* (MMN), eine frühe und automatische sprachrelevante ERP-Komponente, zeigte zwischen 70 und 210 ms nach dem Einsetzen der Phrasenendsilbe, die eine Konstruktion eindeutig machte, eine Interaktion der speicherbezogenen und kombinatorischen Abweichung. Diese Ergebnisse stützen die Hypothese, dass der Abruf und die Kombination sprachlicher Informationen in der Konstruktionsverarbeitung früh, parallel und interaktiv geschehen; die Daten stimmen folglich überein mit der ersten der drei oben formulierten Vorhersagen.

In der *zweiten* Studie wurden MMN-Korrelate bei Zweiwortkonstruktionen vor und nach intensiver Sprachtherapie bei Personen mit chronischer Aphasie nach einem Schlaganfall aufgezeichnet. Die Konstruktionen waren entweder (1) richtig gebildet und bedeutungsvoll, (2) falsch kombiniert, wenn sie die Pronomen-Verb-Kongruenz verletzten, oder (3) sinnfreie Konstruktionen, wenn sie ein „ungespeichertes“ Pseudowort enthielten. Eine klinische Verlaufsdiagnostik mit dem Aachener Aphasietest (AAT) zeigte eine Verbesserung der Sprachfunktionen, die neurophysiologisch mit gesteigerten MMN-Antworten einherging. MMN-Korrelate bei Konstruktionen, die kombinatorisch korrekt waren und „gespeicherte“ Wörter enthielten oder die aus sinnfreien Konstruktionen bestanden, erhöhten sich nach der Therapie signifikant. Im Gegensatz dazu wurden bei falsch kombinierten Konstruktionen keine therapiebezogenen Veränderungen der MMN-Antworten beobachtet. Die MMN-Zunahmen lassen sich mit neuroplastischen Veränderungen im Zusammenhang mit der Konsolidierung der *Cell-Assembly*-Repräsentation von Konstruktionen im menschlichen Kortex erklären; dies gilt auch für sinnfreie Sätze, deren kombinatorische Struktur intakt war. Die Ergebnisse der zweiten Studie belegen die Wiederherstellbarkeit der Konstruktionsverarbeitung durch therapeutische Ansätze im Einklang mit neurobiologischen Funktionsprinzipien des menschlichen Kortex.

In der *dritten* Studie wurden Daten aus einem modellierten neuronalen Netzwerk mit Morlet-Wavelet-Zeit-Frequenz-Analyse ausgewertet. Das Netzwerk replizierte dabei Eigenschaften primärer, sekundärer und assoziativer frontaler, temporaler und okzipitaler Areale des menschlichen Kortex. Zu diesen Eigenschaften zählen sowohl physiologische (assoziatives hebbsches und anti-hebbsches Lernen) als auch neuroanatomische (Konnektivität). Die Instanzen des neuronalen Netzwerks wurden erst trainiert, um das Lernens einfacher Konstruktionen zu simulieren. Daraufhin wurde die Netzwerkaktivität abhängig von der Präsentation gelernter oder nichtgelernter simulierter Konstruktionen verglichen. Die Ergebnisse zeigten eine stärkere oszillatorische Hochfrequenzaktivität für gelernte Konstruktionen und waren deckungsgleich mit elektrophysiologischen Forschungsdaten am Menschen. Erstmalig ließen sich in einem biologisch-realistischen neuronalen Computermodell sprachrelevanter Hirnareale oszillatorische Phänomene beobachten, die auf Konstruktionsverfahren beruhen.

Insgesamt zeichnen die Ergebnisse der hier vorgestellten drei Studien ein kohärentes Bild, das neurowissenschaftliche und konstruktivistische Ansätze zur Sprachverarbeitung verbindet. Zudem bekräftigen die Daten die Annahme, dass Konstruktionen durch speicherbezogene und kombinatorische Mechanismen neuronaler Zellverbände entstehen, die jeweils grundlegende und unterschiedliche Funktionen erfüllen.

List of Publications

This dissertation is based on the following publications:

Lucchese G, Hanna J, Autenrieb A, Miller TM, Pulvermüller F (2017). Electrophysiological evidence for early and interactive symbol access and rule processing in retrieving and combining language constructions. **Journal of Cognitive Neuroscience**. 29:254-266. doi:10.1162/jocn_a_01038.

Lucchese G, Pulvermüller F, Stahl B, Dreyer FR, Mohr B (2017). Therapy-induced neuroplasticity of language in chronic post stroke aphasia: a mismatch negativity study of (a)grammatical and meaningful/less mini-constructions. **Frontiers in Human Neuroscience**. 10:669. doi:10.3389/fnhum.2016.00669.

Garagnani M*, **Lucchese G***, Tomasello R, Wennekers T, Pulvermüller F (2017). A spiking neurocomputational model of high-frequency oscillatory brain responses to words and pseudowords. **Frontiers in Computational Neuroscience**. 10:145. doi:10.3389/fncom.2016.00145.

*__Equal contribution__

List of Abbreviations

AAT = Aachen Aphasia Test

CA = cell assembly

CNS = central nervous system

CVA = cerebro-vascular accident

DCNA = discrete combinatorial neuronal assembly

EEG = electroencephalography

ELAN = early left anterior negativity

ERP/F = event related potential/field

IPC = inferior parietal cortex

LAN = left anterior negativity

LIFG = left inferior frontal gyrus

LQ = laterality quotient

MCA = middle cerebral artery

MEG = magnetoencephalography

MMN = mismatch negativity

MMNm = magnetic mismatch negativity

PSA = post stroke aphasia

Pt. = patient

SD = standard deviation

SE = standard error

SLT = speech language therapy

SOA = stimulus onset asynchrony

STG = superior temporal gyrus

TF = time-frequency

TP = temporal pole

TT = Token Test

1. Introduction

When we read or hear a sentence, we normally grasp the message it entails, usually in an efficient way. This is remarkable considering that the number of sentences that we can produce and understand is potentially unlimited. Although we learn a vast, if inherently limited repertoire of words, we can combine them in accordance with a set of rules in a theoretically unlimited number of ways. These two abilities, the storage of a large number of learned arbitrary symbols (e.g. words) and their rule-based combination into potentially endless higher order structures (e.g. sentences), seem to be peculiar to the human brain (Bouchard, 2015; Chomsky, 1957, 1965; Hurford, 2004; Premack, 2004, 2007). Therefore, any cognitive and neuroscientific account of language perception and of human language in a broader sense must examine these mechanisms.

The words that we know are traditionally defined as lexicon and the rule-based system to combine them as syntax (Chomsky, 1957, 1965; Fodor, 1983; Pinker, 1997). This distinction however does not capture the full range of storage-related and combinatorial mechanisms that are involved in language. On the one hand, combinatorial mechanisms find application to linguistic units within words, e.g. phonemes and morphemes (Estivalet & Meunier, 2015; Jakobson, 1971c; Leminen, Leminen, Kujala, & Shtyrov, 2013; MacGregor & Shtyrov, 2013; Marslen-Wilson, 2007; Say & Clahsen, 2002). On the other hand, recent linguistic approaches suggest that not only complex derived words but also multi-word patterns can be stored as integral units; if this is indeed the case, storage-related mechanisms must extend also above the single-word level (Goldberg & Jackendoff, 2004; Goldberg, 1995, 1996, 2013; Langacker, 2008). The hypothesis that storage-related and combinatorial mechanisms may be at work on linguistic structures of any order, below as well as above single-word-level, is not entirely new (Jakobson, 1971b). Indeed, the idea that storage-related and combinatorial mechanisms, and lexicon and syntax are not segregated in a double dissociated pattern but that the former two act and span orthogonally across the linguistic hierarchical levels formed by morphemes, words, and phrases (Figure 1.1) is compatible with the assumption, shared by the family of linguistic approaches known as construction grammar, that lexicon and syntax are located at the opposite ends of a spectrum (Boas, 2013; Goldberg, 2013; Hoffmann, 2013; Pulvermüller, Cappelle, & Shtyrov, 2013; Stefanowitsch & Gries, 2003), whereas a more biologically precise distinction could, and probably should, be drawn precisely between storage-related and combinatorial mechanisms (Nooteboom, Weerman, & Wijnen, 2002; Pulvermüller et al., 2013).

What is then the relation, if any, between these two mechanisms during language processing and what is their possible neurophysiological basis? Can the neuroscientific investigation of language processing contribute to further the understanding of mechanisms behind constructions in the brain? And can the theoretical framework of construction grammar help in the design and interpretation of experimental work on language? Indeed, if on the one hand neurolinguistic and neurocomputational research has provided some empirical evidence on brain basis of constructions, constructionist approaches are in return providing new perspectives in formulating hypotheses and interpreting experimental results (Allen, Pereira, Botvinick, & Goldberg, 2012; Goldberg, 2013; Pulvermüller et al., 2013). The next paragraphs aim at illustrating that:

- A neurobiological perspective on constructions is consistent with the strong cognitive connotation of construction grammar, grounding it in the brain.

- A constructionist approach to the neurophysiology of language processing can in turn contribute to the advancement of the understanding of models of language comprehension and is suggestive of parallel interactive processing.

- This bidirectional relationship between construction grammar and neurobiology of language can be proficiently tested in healthy subjects, in post stroke aphasia, and in computational models applying neurophysiological methods.

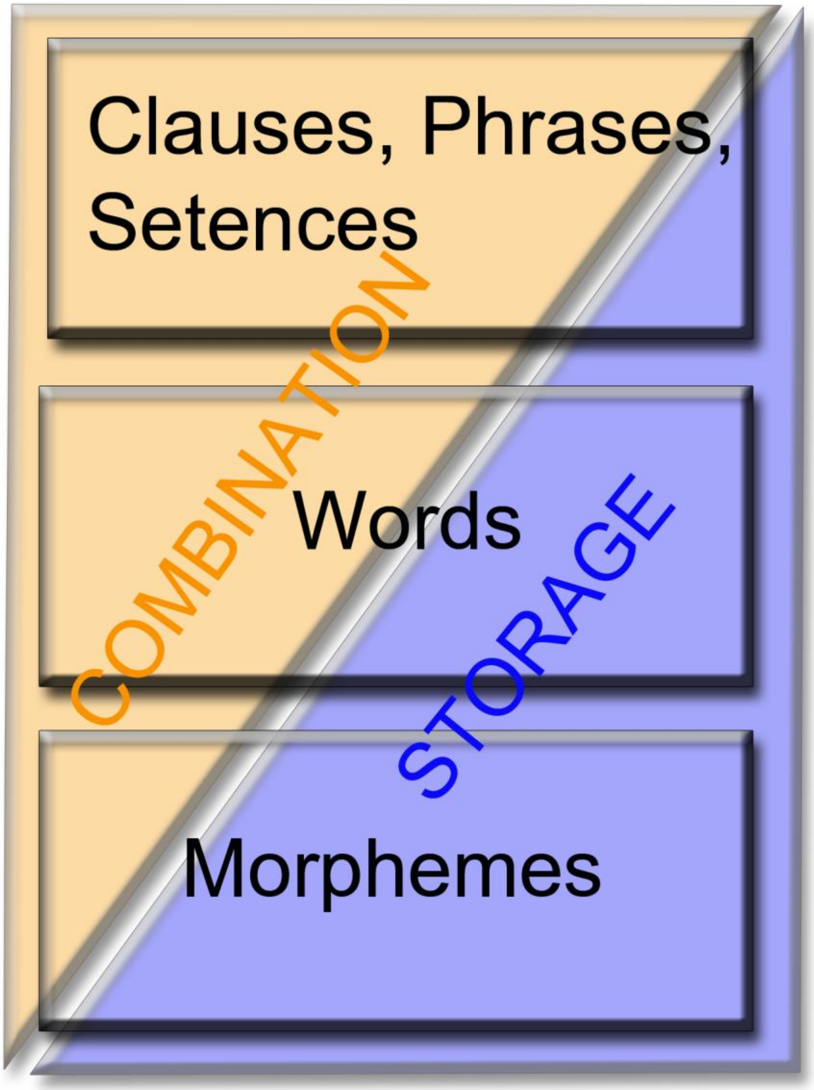


Figure 1.1. A conceptualised representation of the relationship between storage-related and combinatorial mechanisms and linguistic structures of different levels of complexity (morphemes, words, sentences). Possibly the two mechanisms operate across different levels of complexity, without being entirely confined to the lowest (morphemes) or the highest (sentences) ones.

1.1 Brain basis of constructions

Constructions and their relationship with storage-related and combinatorial mechanisms

Constructions are form-meaning pairs with different levels of complexity and abstraction (Goldberg, 1995, 2003, 2013). The idea that language implies the linkage of form with meaning is not recent (Barthes, 1967; de Saussure, 1983; Jakobson, 1971c), however the novelty of constructionist theories lies in extending this association above the single-word-level, so that not only morphemes and words but also more complex and increasingly abstract linguistic structures, like idioms, clauses, and sentences are all considered to be pairs of form and meaning, that is to say constructions (Goldberg, 2013; Hoffmann, 2013). The pairing of form and meaning at all levels of linguistic structure is the core of construction grammar and it is common to all constructionist approaches (Goldberg, 2003, 2013). In particular, the meaning is specifically and univocally linked to the complex form of a multi-word construction in the way neither one nor the other are derivable from the single words, constructions in their own right, that compose the higher-level construction (Boas, 2013; Goldberg, 1996; Stefanowitsch & Gries, 2003). In the words of Goldberg (1995):

> "*Phrasal patterns are considered constructions if something about their form or meaning is not strictly predictable from the properties of their component parts or from other constructions*".

For example, phrases entailing a cause of movement/subject operating on a theme/object along a direction are instances of the Caused Motion construction and exemplify the non-derivability of the form-meaning pair of complex constructions from other constructions, including the therein embedded lower-order ones. Examples like "*Mina sent Mel a book*" (Goldberg, 2013) and "*Pat sneezed the napkin off the table*" (Goldberg, 1995) are both instances of the Caused Motion construction, but while the former contains a verb clearly related to caused motion the latter does not. The verb "to sneeze", albeit semantically somehow related to motion, does not entails the idea of an agent exerting an effect on an object but nevertheless this specific message is conveyed by the phrasal construction as a whole (Goldberg, 2013; Johnson & Goldberg, 2013). Therefore, the constructionist nature of the pattern resides in the fact that its specific structure, its form, is linked to the semantics of caused movement, so that the meaning of the whole is more than just the sum of its lexical parts. Complex and abstract constructions are composed of slots that can be filled according to the intrinsic form of each specific construction (Hoffmann, 2013). The meaning of complex constructions emerges from their correct combination into the higher order structure, that is the correct filling of the slots, and this correct combination constitutes the form to which the correspondent meaning is associated. This compositionality of constructional meaning clearly highlights the relevance of combinatorial processes for constructionist approaches to language (Kay & Michaelis, 2012) and investigating combinatorial mechanisms, together with storage and retrieval that are often seen as the central idea of construction grammar (Bybee, 1998; Bybee, 2006, 2013), is desirable in a construction grammar framework (Duffield & Menn, 2014). Therefore, the neurobiological basis of construction grammar may be better approached by way of the brain mechanisms that underlie storage-related and combinatorial processes.

Construction grammar has a strong cognitive connotation, for it postulates that constructions arise, or, to put it better, are learned, thanks to human cognitive abilities that would constitute the basis for the language function without being language-specific, thus adopting a *usage-based* approach to language acquisition (Goldberg, 2003; Gries, 2013; Lakoff, 1987, 1990; Langacker, 1991; Tomasello, 2003). Indeed recent neuroscientific research indicates that brain networks for language, action, and perception are tightly intertwined and functionally interactive, thus suggesting that language is not an encapsulated system but rather is subserved by broad neurobiological mechanisms. Both storage-related and combinatorial mechanisms, in particular, seemingly operate across the language and the action domains (Grisoni, Dreyer, & Pulvermüller, 2016; Pulvermüller, 2014; Pulvermüller & Fadiga, 2010; Schomers, Kirilina, Weigand, Bajbouj, & Pulvermüller, 2014; Schomers & Pulvermüller, 2016). Hence, storage and combination may be counted among those cognitive mechanisms responsible for the emergence of constructions in the brain. A large body of experimental work in electrophysiology and computation is focussed on these two kinds of mechanism and could help elucidate the neurobiological substrates of language constructions.

Neurobiology of storage-related mechanisms

The brain electromagnetic activity, mainly originating from neural transmission at the synaptic level, can be non-invasively recorded with electro- and magnetoencephalography (EEG; MEG) (Berger, 1929; Birbaumer & Schmidt, 2011; Luck, 2014; Westbrook, 2013). EEG and MEG signals can be analysed quantitatively in different ways. The event-related potentials (ERP) are waveforms that are obtained recording the EEG during repeated instances of an event of interest, or trials, and then averaging the signal across trials. The event-related fields (ERF) are the MEG equivalent of the ERPs (Luck, 2014). Another way of analysing the brain electromagnetic activity is to quantify its pattern of oscillation in different frequency bands, classified, from the lowest to the highest frequency, in delta(< 2 Hz), theta (4-8 Hz) , alpha (9-13 Hz), beta (14-30 Hz), and gamma (> 30 Hz) (Birbaumer & Schmidt, 2011; Lutzenberger, Elbert, Rockstroh, & Birbaumer, 1985; Singer, 1993). When such a frequency analysis is performed considering specific time intervals, thus allowing for time (and phase)-locking to a stimulus, it takes the name of time-frequency (TF) analysis (Herrmann, Grigutsch, & Busch, 2005a; Pfurtscheller & Lopes da Silva, 1999; Roach & Mathalon, 2008).

The ERPs, together with their magnetic equivalent the event related fields (ERF), and TF analysis can be used to investigate the brain activity that reflects the cognitive processes associated with complex stimuli (Donchin, Ritter, & McCallum, 1978; Kaan, 2007; Luck, 2014; Lutzenberger et al., 1985; Pfurtscheller & Lopes da Silva, 1999; Roach & Mathalon, 2008).

Electrophysiological evidence from ERP/F studies suggests that the human brain stores information about meaningful, familiar items in different cognitive domains. For instance, differences in electrophysiological responses to familiar vs unfamiliar stimuli are well established in face and visual shape recognition (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Marini & Marzi, 2016; Schweinberger, Pickering, Jentzsch, Burton, & Kaufmann, 2002; Visconti di Oleggio Castello & Gobbini, 2015). In the linguistic domain, retrieval of stored information is reflected in differences between ERPs to words and pseudowords (Dien, 2009; Endrass, Mohr, & Pulvermüller, 2004; Garagnani, Shtyrov, & Pulvermüller, 2009; Hinojosa, Martí, & Rubia, 2001; Holcomb & Neville, 1990; Korpilahti, Krause, Holopainen, & Lang, 2001; Kutas & Federmeier, 2011; MacGregor, Pulvermüller, van Casteren, & Shtyrov, 2012; Pettigrew et al., 2004; Pulvermüller, Kujala, et al., 2001; Pulvermüller, Shtyrov, & Hauk, 2009; Pulvermüller, Shtyrov, Kujala, & Näätänen, 2004; Rudell, 1991; Shtyrov, Goryainova, Tugin, Ossadtchi, & Shestakova, 2013; Shtyrov, Kujala, & Pulvermüller, 2010; Shtyrov & Lenzen, 2016; Shtyrov & MacGregor, 2016; Shtyrov & Pulvermüller, 2002; Sittiprapaporn, Chindaduangratn, Tervaniemi, & Khotchabhakdi, 2003). ERPs responses are also sensitive to word frequency (Alexandrov, Boricheva, Pulvermuller, & Shtyrov, 2011; Hauk & Pulvermüller, 2004; Kutas & Federmeier, 2011; Sereno, Rayner, & Posner, 1998).

High-frequency oscillatory cortical responses also show differences between meaningful, familiar stimuli and novel, unstored ones (Bertrand et al., 2013; Craddock, Martinovic, & Muller, 2015; Gao et al., 2013; Hassler, Barreto, & Gruber, 2011; Henson, Mouchlianitis, & Friston, 2009; Krause, Korpilahti, Porn, Jantti, & Lang, 1998; Lutzenberger, Pulvermüller, & Birbaumer, 1994; Pulvermüller et al., 1994; Tallon-Baudry, 2009). As in the case of ERPs, high-frequency dynamics reflect recognition of stored items also in the language domain, with meaningful stored stimuli consistently inducing stronger spectral responses than unstored symbols, such as pseudowords (Canolty et al., 2007; Eulitz et al., 1996; Krause et al., 1998; Lutzenberger, Pulvermüller, & Birbaumer, 1994; Mainy et al., 2008; Pulvermüller, Eulitz, et al., 1996; Pulvermüller et al., 1994). Semantic aspects of stored linguistic symbols seem to be reflected in different cortical distribution of high-frequency oscillations and their long-range synchrony across distant brain areas (Pulvermüller, Preissl, Lutzenberger, & Birbaumer, 1996; Weiss & Mueller, 2013).

These differences in the neuronal activity elicited by stored vs unstored linguistic items, as shown by ERPs and EEG oscillations, can be explained by way of the neurobiological concept of ***cell assembly*** (Braitenberg, 1978a; Hebb, 1949; Pulvermüller, 2002; Pulvermüller & Mohr, 1996). A cell assembly is a set of neurons that are tightly connected by excitatory links at the synaptic level. The strength of these excitatory links is such that activation of subsets of the cell assembly can easily lead to full ignition of the whole set, i.e. firing of all neurons of the set. These strong connections can arise thanks to the principle of Hebb (1949):

> *“When an axon of cell A… excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency, as one of the cells firing B, is increased”*

or, to condense the thought to an aphorism, “*neurons wire together if they fire together”* (Lowel & Singer, 1992). On the other hand, excitatory links between neurons which are infrequently active together tend to weaken, a form of negative modulation called anti-hebbian learning (Földiak, 1990; Frégnac, 2003). Remarkably, these theoretical principles have solid biological underpinnings which have been well-established experimentally thorugh research showing the capability of synapses to both potentiate and depress their efficiency in the long term, processes known as Long Term Potentiation (LTP) and Long Term Depression (LTD), respectively (Kandel, 2000). The cell assemblies emerge thanks to synaptic plasticity.

Pulvermüller’s cell assembly theory of language implies that meaningful items are stored in the human brain in form of cell assemblies, also referred to as word webs (Pulvermüller, 2001, 2002), which arise by way of exposure to language and active usage of it, because of consistent, repeated co-activation of the neurons that respond to the perceptive and action-related features of linguistic symbols and of the ones that are activated by the features of the semantic content (Pulvermüller, 1999, 2001; Pulvermüller & Fadiga, 2010). Unstored items lack the neuronal representations constituted by the cell assemblies, and indeed the differences in the electrical brain activity, as indexed by high-frequency oscillations and ERPs, for stored vs. unstored symbols strongly support this view (Pulvermüller, 2001, 2007; Pulvermüller, Kujala, et al., 2001; Pulvermüller et al., 2009) and further support originates from computational research simulating neural networks in the human brain. Crucially, anatomically accurate simulations conducted in computational models implementing hebbian and anti-hebbian learning confirm the emergence of cell assemblies as a mechanism for storing information in the brain and replicate the ERP/F results from electrophysiological research, thus providing a mechanistic link between the biological theory and the ERP/F evidence (Garagnani & Pulvermüller, 2011, 2016; Garagnani, Shtyrov, et al., 2009; Garagnani, Wennekers, & Pulvermüller, 2007, 2008, 2009). It is noteworthy though that to date a replication of the oscillatory storage-related findings in a neurobiologically realistic computational model is still missing.

In light of the evidence for storage-related mechanisms in the brain, it is easy to see how constructions, that are sign-meaning pairs, can be biologically stored, and indeed some ERP/F studies found brain responses that suggest whole-form storage in the brain, possibly in form of cell-assembly, also for some instances of complex derived words (Hanna & Pulvermüller, 2014; MacGregor & Shtyrov, 2013) and even for multi-word constructions (Cappelle, Shtyrov, & Pulvermüller, 2010). Additional evidence in this direction comes from other neuroimaging methods (Allen et al., 2012) and from behavioural research (Johnson & Goldberg, 2013).

Neurobiology of combinatorial mechanisms

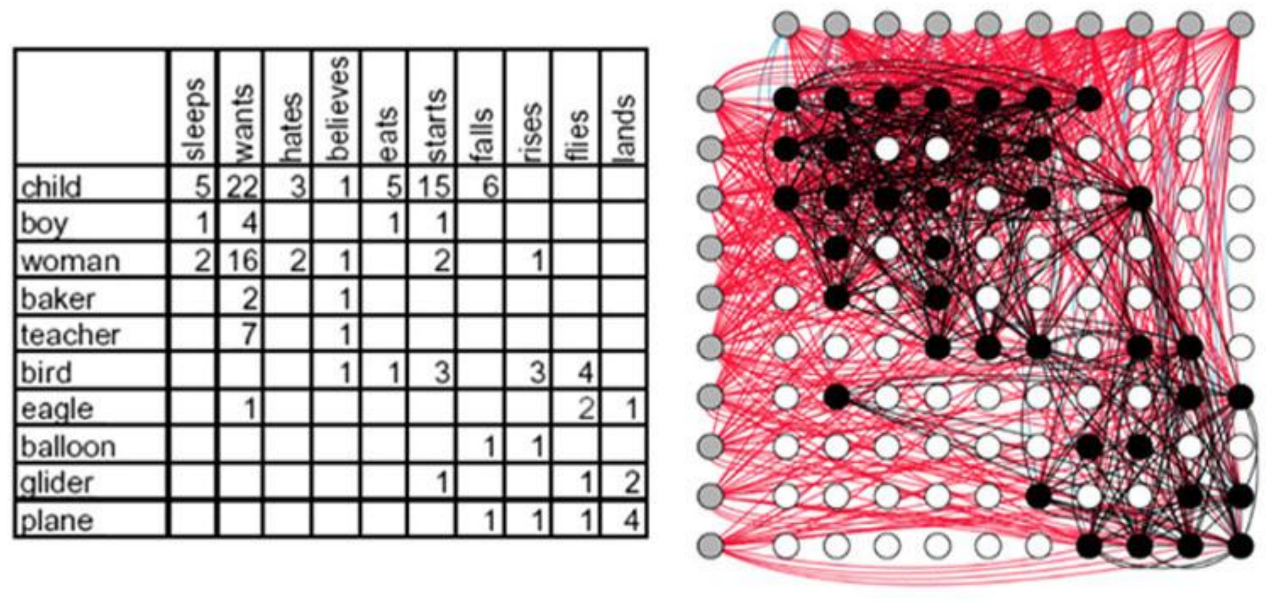
ERP/Fs elicited by words that are not presented in isolation but are embedded in a context can also reflect if the words do not fit the context, either semantically (Gunter, Friederici, & Schriefers, 2000; Kuperberg, 2007; Kutas & Federmeier, 2011; Kutas & Hillyard, 1980; Kutas & Hillyard, 1984; Menning et al., 2005) or syntactically (Coulson, King, & Kutas, 1998; Deutsch & Bentin, 2001; Friederici, Hahne, & Mecklinger, 1996; Gunter & Friederici, 1999; Gunter et al., 2000; Hahne & Friederici, 2002; Hanna, Mejias, Schelstraete, Pulvermuller, et al., 2014; Hasting & Kotz, 2008; Hasting, Kotz, & Friederici, 2007; Kuperberg, 2007; Menning et al., 2005; Neville, Nicol, Barss, Forster, & Garrett, 1991; Pulvermüller & Assadollahi, 2007; Pulvermüller & Shtyrov, 2003; Pulvermüller, Shtyrov, Hasting, & Carlyon, 2008; Shtyrov, Pulvermüller, Näätänen, & Ilmoniemi, 2003).

The electrophysiological evidence on combinatorial mechanisms can be interpreted in light of the emergence of cell assemblies in the brain, as it is the case for storage-related mechanisms. Rule-based combinatorial linguistic phenomena, for instance both local and nonlocal syntactic relationships, would be implemented in the brain by way of discrete combinatorial neuronal assemblies (DCNAs), which are high-order ensembles of neuronal cells that link together cell assemblies for unitary stored items, and therefore are defined *combinatorial* (Pulvermüller, 2002, 2010; Pulvermüller & Assadollahi, 2007; Pulvermüller &

Knoblauch, 2009). These neuronal assemblies are characterised by temporal sensitivity to sequence of activations of their constituents, i.e. lower order cell assemblies,(Pulvermüller, 2003) and by *discrete* states of activity, including inactivity, full ignition, inner oscillatory reverberation, and sub-threshold activation or priming of constituents. The sensitivity to order of activations of the constituents would be conferred to the DCNAs by sequence sensitive neurons or *sequence detectors*. (Pulvermüller, 2002, 2010; Pulvermüller et al., 2013). The correct sequence of retrieval of stored linguistic units – that is to say a specifically ordered activation of their cell assembly representations in the DCNA – would then be accompanied by lower overall brain electrical activity because of the priming of successive representations by the preceding ones, with less activity needed to reach the threshold for full ignition. Incorrect sequences in combinatorial violations would not operate any priming and the retrieval of stored lexical units presented in combinatorial rule-breaking context would therefore generate different patterns of brain activity than well-combined word strings, thus explaining differences in ERP responses (Pulvermüller, 2010; Pulvermüller & Assadollahi, 2007; Pulvermüller & Shtyrov, 2003; Pulvermüller et al., 2008). The links provided by DCNAs for both adjacent or distant elements in complex constructions would then be underpinned by the very same neuronal mechanism (Pulvermüller, 2010; Pulvermüller et al., 2013). The binding of stored units operated by DCNAs and sequence detectors can be operated in the form of synchronisation of oscillatory activity of the unitary stored components. And indeed oscillatory dynamics appear to reflect, not only retrieval of unitary stored linguistic information, as discussed above (see Section 1.1, *Neurobiology of storage-related mechanisms*), but also language processing at the sentence-level (Bastiaansen & Hagoort, 2006, 2015; Bastiaansen, Magyari, & Hagoort, 2010; Lewis, Wang, & Bastiaansen, 2015; Weiss & Mueller, 2003; Weiss & Mueller, 2013; Weiss et al., 2005).

Like unitary cell assembly representations of stored items, DCNAs are not abstract entities but biological ones and their emergence is underpinned by realistic principles of neural functioning. Once again computational modelling provides compelling evidence mechanistically linking theoretical hypotheses to experimental data. A simulation in a network capable of hebbian associative learning and pre-equipped with sequence detecting units shows that presentations of noun-verb pairs built out of a set of ten nouns and ten verbs (e.g., *balloon* *rises*; *child sleeps*; …), based on the frequency of their co-occurrence in actual language, induces the emergence of DCNAs, i.e. the learning of combinatorial principles (Pulvermüller & Knoblauch, 2009). Interestingly, the DCNAs in the network show, depending on threshold of activation, a mixed lexico-syntactic-semantic relevance, in the way they form strengthened links not only between word categories (verb-noun) but also between lexical items with shared semantic properties (e.g. flying entities with flight-related verbs) (Figure 1.2).

This simulation provides a mechanistic explanation for the emergence of combinatorial mechanisms for language in the brain by way of the general biological principles underlying the functioning of the human cortex, thus supporting the hypothesis of usage-based language acquisition assumed by constructionist theory (Goldberg, 2003; Pulvermüller et al., 2013; Tomasello, 2003). DCNAs in the brain can link sets of neuronal representations of stored linguistic items into higher order ones, just like smaller constructions are embedded into more complex and abstract ones (Hoffmann, 2013; Pulvermüller et al., 2013).



	sleeps	wants	hates	believes	eats	starts	falls	rises	flies	lands
child	5	22	3	1	5	15	6			
boy	1	4			1	1				
woman	2	16	2	1		2		1		
baker		2		1						
teacher		7		1						
bird				1	1	3		3	4	
eagle		1							2	1
balloon							1	1		
glider						1			1	2
plane							1	1	1	4

Figure 1.2. Emergence of DCNAs for noun–verb sequences in a neural network simulation (Pulvermüller & Knoblauch, 2009). The matrix on the left presents frequency of co-occurrence of 20 English nouns and verbs obtained from the British National Corpus, BNC (in number of word pair occurrences per 100 million words). On the right are presented the lexical units (gray), the sequence detectors (black and white), and the links between them , which were strengthened by learning. Sequence detectors whose connections with lexical units were strengthened during learning (red links) are represented by black circles. Black links represent strengthened connections between pairs of sequence detectors. At the top left and bottom right, two discrete combinatorial neuronal assemblies, DCNAs, have formed. Note how the DCNAs provide not only syntactic but also semantic linkage between verbs and nouns related to living entities, as well as between verbs and nouns related to flying (adapted from Pulvermüller & Knoblauch, 2009).

1.2 Models of language processing

If the neuroscience of language may contribute to the elucidation of the brain mechanisms underpinning the acquisition and usage of linguistic constructions, what could be in turn the contribution of a constructionist approach to further the understanding of the neurophysiology of language processing? In order to attempt to answer this question one must examine psycho- and neurolinguistic models[1] of language processing and the neurophysiological evidence advocated in their support.

Language understanding implies real-time usage of different sources of information including what is traditionally defined in linguistics as lexical and syntactic information. The question of how and when various bits of information are used has been the object of extensive psycholinguistic and neurophysiological research that can be divided in two kinds of models of language comprehension, one is characterized by sequential, cascaded steps and the other one advocates simultaneous and parallel integration of types of information. The following paragraphs describe these two families of models with the neurophysiological body of evidence on the topic and how a constructionist approach could help in orienting and interpreting experimental investigations on language comprehension.

The first of these two families of models envisages language comprehension as an ordered sequence of steps, with each step corresponding to the appraisal of a specific kind of linguistic information. In this cascaded, serial model one type of information is processed first and in isolation, and can be interpreted as leading the comprehension process, in the sense that only if this first step reaches successful completion the next one can be initiated (Fedorenko, Piantadosi, & Gibson, 2012). The predominant view among the "cascaded" theories of language comprehension is that the first step consists in phrase structure building, based on word-category syntactic information (Ferreira & Clifton, 1986; Frazier, 1987; Frazier & Fodor,

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[1] The term "*model*" indicates in the context of this paragraph a conceptual schematic representation of the time course and relationships of the various aspects of a process, i.e. language comprehension, and is not to be confused with computational reproductions of brain structures designed and programmed to replicate some brain functions, even though the two concepts can be somehow related. The latter meaning is implied when referring to computational research elsewhere in the present work (see for instance 1.1 in this chapter and chapter 4).

1978; Fromkin, 1973; Garrett, 1976). The other family of theories accounting for language comprehension sees it as an interactive parallel process in which all types of information are available and used at any point in time from early on. These models entail the mutual interplay of lexico-semantic and syntactic appraisal from the very first moment onwards (Boland, 1997; MacDonald, Pearlmutter, & Seidenberg, 1994; Marslen-Wilson & Tyler, 1980; Townsend & Bever, 2001; Trueswell, Tanenhaus, & Garnsey, 1994).

Experimental psycholinguistic evidence in support of both accounts of language comprehension originates mainly from behavioural studies designed to assess the kind of linguistic information – either syntactic, or lexico-semantic, or both – used in order to interpret ambiguous items in a sentence (Fedorenko et al., 2012; Frazier & Clifton, 1996; MacDonald, 1993; Tanenhaus & Trueswell, 1995). This experimental approach unfortunately does not provide direct evidence about the actual time course of language processing in the brain, and therefore an accurately timed highly resolved account of the physiology of language understanding must be pursued with different methods.

Cascaded processing

As discussed in Section 1.1., ERP/Fs allow for the examination of the electrical activity in the brain and high temporal precision is a peculiarity of these electrophysiological techniques. ERP/Fs make possible to investigate cognitive processes as they unfold in the brain (Luck, 2014; Woodman, 2010) and specific ERP/F components seem to index processing of specific types of linguistic information at specific time latencies (see Section 1.1 and Kaan, 2007; Kutas & Federmeier, 2007; Kutas, Van Petten, & Kluender, 2006; Pulvermüller, 2007); therefore, they appear to be the ideal tool to investigate the actual time course of language processing and models of language comprehension.

The early left anterior negativity (ELAN) is an ERP that owes its name to its early latency - around 80 to 200 ms after presentation of the critical word - and to the fact that it typically shows maximum amplitude at electrodes placed on the left anterior region of the scalp. The ELAN indicates whether or not the critical word fits into the syntactic context provided by the sentence within which it is embedded (Deutsch & Bentin, 2001; Friederici et al., 1996; Friederici, Pfeifer, & Hahne, 1993; Hasting & Kotz, 2008; Neville et al., 1991). The ELAN, or more precisely the ELAN increase associated with combinatorial word category violations, is interpreted as an index of disruption of word-category based phrase-structure building (Friederici, 2002; Friederici & Weissenborn, 2007; Hahne & Friederici, 2002) and is considered to be related to the left anterior negativity (LAN), which is slightly later (300-500 ms) and is sensitive to a wider range of combinatorial syntactic violations, including morphosyntactic ones (Coulson et al., 1998; Steinhauer & Connolly, 2008; Swaab, Ledoux, Camblin, & Boudewyn, 2012).

A third language-related ERP component, the N400, emerges in the same latency range of the LAN, but is known to reflect semantic and lexical violations (Kutas & Federmeier, 2011). Semantic incongruences elicit a larger N400 compared with words that are coherent with the context (Kutas & Hillyard, 1980; Kutas & Hillyard, 1984). The N400 also reflects lexical access to stored items. Meaningless pseudowords elicit larger N400 responses compared with familiar meaningful words (Holcomb & Neville, 1990) and its amplitude inversely correlates with word frequency (Kutas & Federmeier, 2011). The N400 is therefore sensitive to both storage-related lexical semantics and to combinatorial semantics.

A later, positive ERP waveform at about 600 ms, the P600, reflects a range of combinatorial violations, both syntactic and semantic ones (Gunter et al., 2000; Kuperberg, 2007; Osterhout & Holcomb, 1992).

Ordering these components and the processing of the specific kind of linguistic information to which they seem to be related in accordance to their respective latencies is the basis of a three-phase neurophysiological model of language comprehension, that is closely related to the psycholinguistic syntax-first serial models (Friederici, 2002, 2011). In this model so-called phase 0 (0 to 100 ms) is dedicated to basic perceptual and sub-lexical analysis and is followed by phase 1 (100 to 300 ms), which allocates the building up of the phrase structure on the basis of category information, Disruption of this word category dependent process yields the ELAN effect. Phase 2 (300 to 500 ms) sees the independent non-interactive occurrence of both morphosyntactic appraisal and lexico-semantic integration, reflected by the LAN and N400, respectively. Interaction of syntactic and semantic processes only happens during phase 3 (500 to 1000 ms) and anomalies at this stage result in the P600 effect, which is affected by semantic and syntactic violations (Gunter et al., 2000). Such a model encompasses aspects of different psycholinguistic theories, yet it is essentially a syntax-first serial, modular model: a cascaded sequence of steps, among which the later ones can entail parallel processing. The purely syntactic word-category-based first step is followed by activation of parallel non-interactive morphosyntactic and lexico-semantic streams of processing, and interaction is finally allowed only at P600 latencies, so that both "autonomous processing and interactive processing hold in principle but describe different processing phases during language comprehension (i.e. early versus late)" (Friederici & Weissenborn, 2007). The presence of the syntactic ELAN effect and the concomitant absence of a N400 response for combined word-category and semantic double violations have been interpreted as further evidence for cascaded syntax-first models of sentence processing (Friederici, 2002; Friederici, Steinhauer, & Frisch, 1999).

Yet a large body of evidence seems to run afoul of the above mentioned three-phase syntax-first serial model. First, some methodological concerns regarding the ELAN suggest that it may be heavily affected by spill-over and offset effects from context (Steinhauer & Drury, 2012), thus questioning the reliability of this specific syntactic index that precedes the N400 and the LAN and constitutes the neurophysiological "backbone" of phase 1 of the three-phase syntax-first model. At the same time, the absence of a N400 for semantic violations in case of concomitant phrase structure violations – a phenomenon that is sometimes called the *blocking* or *licensing* effect of word category on semantic processing (Friederici et al., 1999; Friederici & Weissenborn, 2007; Hahne & Jescheniak, 2001; Steinhauer & Drury, 2012; Zhang, Yu, & Boland, 2010) and is taken as evidence for syntax-first serial processing – fails to manifest itself depending on the experimental tasks and designs (Gunter & Friederici, 1999; Hahne & Friederici, 2002; van den Brink & Hagoort, 2004; Yang, Wu, & Zhou, 2015; Yu & Zhang, 2008; Zhang et al., 2013; Zhang et al., 2010).

Moreover syntax-first views of language comprehension like the three-phase model allocate combinatorial processes, specifically syntactic ones, very early during online language processing without providing a satisfactory account of retrieval of lexico-semantic information stored as form-meaning pairs. Even though a number of studies report on syntax-semantics interaction effects in the N400 time range, that is to say, earlier than the three-phase model would allow (Guajardo & Wicha, 2014; Hagoort, 2003; Malaia & Newman, 2015; Palolahti, Leino, Jokela, Kopra, & Paavilainen, 2005; Ye, Luo, Friederici, & Zhou, 2006), nevertheless they do not address the storage *vs* combinatorial aspects of language processing, which may both contribute to various degrees to both syntactic and semantic processing. Furthermore, much of the psycholinguistic evidence for interactive parallel processing suggests that both storage-related word comprehension and combinatorial context integration happen very early (Marslen-Wilson & Tyler, 1975) and semantic judgement can already be formulated and made manifest within 400 ms, thus suggesting that the N400 time range it may actually correspond to a post-understanding stage (Hauk, Coutout, Holden, & Chen, 2012). Brain indices of language processing at around 400 ms and later therefore may not be optimal for research meant to evaluate the timing and the cascaded or parallel nature of stored symbol retrieval and combinatorial processes, which must be investigated with earlier language-related ERP/F responses.

Parallel processing

A large body of ERP/F research shows very early retrieval and combination of linguistic information. Indeed, much of the neurophysiological evidence on stored-form lexical retrieval mentioned above (see Section 1.1, *Neurobiology of storage-related mechanisms*) originates from studies (Alexandrov et al., 2011; Cappelle et al., 2010; Endrass et al., 2004; Hanna & Pulvermüller, 2014; Korpilahti et al., 2001; Pettigrew et al., 2004; Pulvermüller, Kujala, et al., 2001; Pulvermüller et al., 2009; Pulvermüller et al., 2004; Shtyrov et al., 2013; Shtyrov & Pulvermüller, 2002) on a very early (50-250 ms) language-related component, the mismatch negativity (MMN, Pulvermüller & Shtyrov, 2006). The MMN is an event related ERP/F (magnetic MMN or MMNm in case of MEG, Tervaniemi et al., 2005) that is elicited by the occurrence of a rare stimulus (deviant) amongst a more frequently repeated one (standard), does not require attention, and was originally identified in response to deviance in basic acoustic properties (Näätänen & Alho, 1995; Näätänen, Gaillard, & Mantysalo, 1978).

Classically defined as an index of deviance detection in the brain, the MMN is not elicited by any stimulus which is not preceded by a repeated standard and is obtained by subtracting the averaged response to the standard from the one to the deviant. Moreover, the more familiar the deviant stimulus is, the stronger is the MMN that it elicits (Naatanen, Paavilainen, Rinne, & Alho, 2007). In other words the mismatch response elicited by the deviant depends on the stored memory trace for the deviant itself and this allows it to be used specifically to test the presence and strength of memory traces for words (Alexandrov et al., 2011; Pulvermüller, Kujala, et al., 2001; Shtyrov & Pulvermüller, 2002). Words elicit larger MMNs as compared to pseudowords because of the latter lacking a memory trace in form of cell assembly representation, as already discussed in Section 1.1. In addition, the MMN reflects not only storage-related mechanisms but also combinatorial processes. MMN linguistic experiments consistently show that combinatorial violation, specifically syntactic ones, elicit larger responses than well-combined strings (Hanna, Mejias, Schelstraete, Pulvermuller, et al., 2014; Hanna, Shtyrov, Williams, & Pulvermuller, 2016; Hasting et al., 2007; Herrmann, Maess, Hasting, & Friederici, 2009; Pulvermüller & Assadollahi, 2007; Pulvermüller & Shtyrov, 2003; Pulvermüller et al., 2008; Shtyrov et al., 2003) and this evidence supports the DCNAs biological model of combinatorial mechanisms in the brain (see Section 1.1, *Neurobiology of combinatorial mechanisms* and Pulvermüller, 2010; Pulvermüller et al., 2013). The MMN is then a very early index of both storage-related and combinatorial linguistic processes in the brain.

A further advantage of the MMN is that it is an automatic response and does not require subjects to pay attention to the stimuli nor to carry out any tasks or active judgements. Active tasks are normally part of N400 and P600 paradigms and, as also discussed above in regard to cascaded models of language understanding, they can significantly affect experimental results (Friederici & Weissenborn, 2007; Gunter & Friederici, 1999; Hahne & Friederici, 1999; Hahne & Friederici, 2002; Osterhout & Mobley, 1995; Schacht, Sommer, Shmuilovich, Martienz, & Martin-Loeches, 2014). On the contrary, the automaticity of the MMN paradigms for investigating storage-related and combinatorial mechanisms may provide information on language processes that are independent from the subjects' active judgement of linguistic materials, and in this sense arguably closer to every-day language understanding.

Crucially, MMN linguistic effects are not affected by concerns raised in regard to spill-over and uncontrolled context effects confounding the ELAN responses (see discussion on cascaded models above and Steinhauer & Drury, 2012) and from undesired variability due to differences in physical and psycholinguistic properties of the critical stimuli themselves (Penolazzi, Hauk, & Pulvermüller, 2007). MMN studies on storage-related and combinatorial language mechanisms adopt orthogonal designs in order to control for both context and critical MMN-eliciting stimuli and in such studies it is even possible to elicit the responses to stored and unstored and to well- and ill-combined strings using identical syllable recordings (Cappelle et al., 2010; Pulvermüller, Kujala, et al., 2001; Pulvermüller & Shtyrov, 2006; Shtyrov et al., 2003). The orthogonality of context and critical stimuli to the linguistic factors under investigation rules out confounders that might affect other language ERPs. The price to pay for such an optimal control of undesired variability and independence from attentional load is the frequent repetition of standard and critical deviant stimuli that is intrinsic to MMN designs, which may therefore be prone to repetition effects and have a limited ecological validity. In spite of this potential objection, early linguistic effects originally found in highly controlled MMN studies have been confirmed by studies adopting less repetitive designs but still properly controlling for undesired variability (MacGregor et al., 2012; Shtyrov & MacGregor, 2016). The MMN offers a solution to many of the issues affecting studies on other language-related ERPs and it reflects specifically both storage-related and combinatorial properties of language processing at very early latencies.

The evidence from ERP research on early linguistic components strongly suggests that both retrieval and combination of stored linguistic symbols happen in parallel and almost instantaneously from the very beginning of language comprehension. Yet a specific electrophysiological investigation on the interaction of the two processes at latencies earlier than 200 ms is still missing and the MMN seems to be the optimal means with which to fill this gap. Adopting a constructionist theoretical framework may help in formulating hypotheses and interpreting the results of such an experimental investigation, as the next section aims at illustrating.

Construction grammar suggests early parallel interactive language processing

The MMN and other early ERP/Fs show how retrieval and combination of linguistic information occur in the same early time range (< 200 ms) and are explained by the cell assembly theory of language, which is grounded in neurobiological principles acting at cellular and subcellular level in the central nervous system (CNS) and which takes neuronal groups with strong functional and structural links as the building unit of the language ability. Constructions, whose emergence in the brain is consistent with the same neurobiological principles behind early ERP responses, are by definition linguistic structures of various degrees of complexity (see 1.1.), with the implication that linguistic information needs to be successfully stored/retrieved and combined at the very same time to allow for full understanding of any construction. Therefore, it appears that both recent neurophysiological evidence on language processing and constructionist theory not only might share the same neurobiological foundations, but also strongly suggest early parallel and interactive retrieval and combination of linguistic information in the brain during language understanding. The natural consequence of adopting a constructionist framework is to predict simultaneity and interaction of storage-related and combinatorial mechanisms during language processing. The obvious choice to test this prediction is the MMN.

1.3 Testing construction processing in post stroke aphasia

The argument for increased explanatory power offered by multidisciplinary linguistic and neuroscientific approaches for understanding language mechanisms, like storage-related and combinatorial mechanisms, can gain strength from the investigation of clinical conditions affecting language abilities, and specifically post stroke aphasia (PSA). Indeed, aphasia has long been considered a disorder that presents a means for ”dissecting” the language function through the examinination of selective impairments and their relation to specific brain lesions (Churchland, 1989; Freud, 1891; Jakobson, 1964, 1971a; Lichteim, 1885; Pulvermüller, 2002; Ropper & Brown, 2005). A theoretical multidisciplinary, i.e. both linguistic and neurobiological, approach can improve the understanding of the pathophysiology of the impairments and therefore also the efficacy of treatment (Berthier & Pulvermüller, 2011; Cahana-Amitay, Albert, & Oveis, 2014; Pulvermüller, 1995; Pulvermüller & Berthier, 2008). If the exchange between construction theory and experimental neurophysiology can result more powerful than other apporaches in investigating language in the brain, then post stroke aphasia is an excellent field to probe its potential.

Neurobiology insights into language improve therapy of post stroke aphasia

Aphasia is an acquired impairment of language, often consequence of a stroke. Language disturbances cause a high grade of disability and among them post stroke aphasia (PSA) shows high incidence rates. The result is that PSA is a highly-frequent, highly-disabling clinical condition that produces a heavy burden both at individual and social level (Berthier, 2005; Engelter et al., 2006; Pedersen, Vinter, & Olsen, 2004).

Major progress in aphasia rehabilitation originated with the application of neurobiological insights on language into clinical practice. In particular, it seems that shaping rehabilitative intervention according to biological principles of neuronal functioning like associative hebbian learning can increase efficacy of treatment (Berthier et al., 2009; Berthier & Pulvermüller, 2011). Hebbian learning, which also appears to play a relevant role as a biological basis for the emergence of constructions in the brain (see Section 1.1), implies that for the strength of the connections between neuronal assemblies to increase, the assemblies need to be frequently active at the same time, and infrequently active at different times in order to minimise anti-hebbian learning (Frégnac, 2003; Hebb, 1949). Therefore, administering rehabilitation therapy at high intensity should increase the correlation and the coincidence of activation of the neural networks responsible for language processing thus strengthening their connections and fostering recovery of language and communication functions in PSA (Berthier & Pulvermüller, 2011; Pulvermüller & Berthier, 2008). Indeed, speech and language therapy seems to be especially effective for PSA, even at the chronic stage, if it is provided with high intensity, that is to say for more than 5 hours per week (Berthier & Pulvermüller, 2011; Brady, Kelly, Godwin, Enderby, & Campbell, 2016; Meinzer, Elbert, Djundja, Taub, & Rockstroh, 2007; Pulvermüller, Neininger, et al., 2001; Sickert, Anders, Münte, & Sailer, 2014; Stahl, Mohr, Dreyer, Lucchese, & Pulvermüller, 2016).

The same neurobiological principles, i.e. hebbian learning and cell assembly formation, that underpin storage-related and combinatorial mechanisms and possibly usage-based emergence of language constructions in the brain, seem to foster recovery of the language function in cases of chronic PSA. Therefore, a constructionist approach to language processing and improvement thereof in aphasic patients could offer further insights into both constructions in the brain and the treatment of aphasia. The question would then be how experimentally to investigate the brain activity that reflects retrieval and combination of linguistic information in aphasic patients exposed to constructions before and after rehabilitation therapy.

The MMN in post stroke aphasia

In the previous sections it was discussed how the brain basis of constructions can be considered to be tightly linked to storage-related and combinatorial mechanisms (in particular see Section 1.1), as well as how both of these mechanisms are reflected, and can be experimentally investigated, using the MMN (see Section 1.2). The answer to the question of how to investigate construction processing in aphasia is thus easily answered adopting MMN paradigms and designs.

The MMN is particularly well suited to test patients that suffer from neuropsychiatric and cognitive impairments. Altered MMN(m) responses, mainly to elementary acoustic stimuli like tones but also to vowels or words, have been reported in schizophrenia, autism spectrum disorder, depression and bipolar disorder, various forms of dementia, specific language impairment (SLI) and number of other neuropsychiatric diseases (Abdeltawwab & Baz, 2015; Andersson, Barder, Hellvin, Løvdahl, & Malt, 2008; Baldeweg & Hirsch, 2015; Brønnick, Nordby, Larsen, & Aarsland, 2010; Davids et al., 2011; Light & Braff, 2005; Ludlow et al., 2014; Näätänen et al., 2012; Näätänen et al., 2011; Näätänen, Sussman, Salisbury, & Shafer, 2014; Pekkonen, 2000; Pekkonen et al., 2002; Restuccia, Vollono, Scaloni, Buccelletti, & Camardese, 2015; Roberts et al., 2011).

The automaticity of the MMN is an advantage in examining brain activity in healthy subjects and it is even more so when it comes to patients, who could experience higher difficulties in engaging in active tasks. As discussed in Section 1.2, the independence of the MMN from attentional load is also particularly convenient for the testing of language processing. Thus, the MMN appears to be an ideal tool for research on language disorders. MMN research on aphasic patients shows relatively robust responses to non-linguistic auditory stimuli, such as pure tone deviants, along with reduced responses to linguistic material, when compared to healthy controls (Aaltonen, Tuomainen, Laine, & Niemi, 1993; Auther, Wertz, Miller, & Kirshner, 2000; Becker & Reinvang, 2007; Csépe, Osman-Sági, Molnár, & Gósy, 2001; Ilvonen et al., 2004; Peach, Rubin, & Newhoff, 1994; Pettigrew et al., 2005; Wertz et al., 1998), but recent studies comparing the processing of words *vs* pseudowords show that when patients undergo intensive speech and language therapy (SLT), the MMN(m)responses to actual words, in contrast to pseudowords, significantly increase in parallel to language performances, as clinically measured (MacGregor, Difrancesco, Pulvermüller, Shtyrov, & Mohr, 2015; Mohr et al., 2016).

The MMN not only reflects both storage-related and combinatorial mechanisms of language processing but is also sensitive to therapy-induced cortical plasticity in aphasic patients undergoing language rehabilitation. This is not surprising because these phenomena seem to be all underpinned, at least in part, by the same neurobiological properties of the human brain, i.e. associative learning and hebbian plasticity. No studies to date seem to have used the MMN to examine changes in brain processing of complex constructions above single word levels during aphasia therapy, thus adding combinatorial aspects of construction processing to the picture. All these considerations indicate the MMN to speech stimuli as an ideal experimental tool for investigating processing of complex constructions, i.e. above single-word level, in chronic aphasic patients treated with intensive language therapy.

1.4 Overview of the present work

The present work aims at examining language processing in a constructionist framework using electrophysiological methods on the healthy, the aphasic, and the modelled human brain, in order to add an original contribution to the current body of evidence in each of the three different domains (normal, pathological, simulated language processing). As discussed above, early language-related ERPs suggest and constructionist approaches predict early parallel and interactive retrieval and combination of linguistic information in order to successfully match the form and the meaning of a construction in the brain. Despite this indication, an accurately controlled electrophysiological study to test this prediction seems to be missing. Chapter 2 reports precisely this kind of electrophysiological investigation into construction processing in the healthy human brain.

Cell assembly consolidation seems to underpin not only the emergence of constructions in the healthy brain but also language recovery in post stroke aphasia, and therefore a constructionist approach to the electrophysiological investigation on recovery of language ability in aphasic patients who are undergoing intensive language therapy may improve understanding of the biological mechanism promoting the recovery and at the same time may provide further evidence on the neurobiology of constructions. Such an investigation is described in Chapter 3.

The electrophysiological research on language processing is supported, as seen in Section 1.1, by a number of computational studies that clearly replicate the EEG/MEG findings and help link experimental data to neurobiological theories by providing a mechanistic explanation for the emergence of cell assembly in the brain as means of storing/retrieving and combining information to build up constructions. To date such models have provided insights into ERP/Fs results but data from computational models simulating brain activity during construction processing have not yet been examined in the time-frequency domain. Replicating the oscillatory patterns of activity seen in the human brain with a neurobiologically accurate model would provide further support for the cell assembly theory as biological basis of language and constructions. This is the aim and focus of Chapter 4.

The general hypothesis on which the present work is built is that constructions emerge as form-meaning pairs in the brain thanks to the formation and consolidation of cell assemblies that can form links of variable strength, act as units for the storage of information, and variously combine with one another. If such a hypothesis is true, then language processing in the healthy brain must be an interactive, parallel processing; computational models built on the same principles that allow for cell assembly formation must simulate the actual activity in the human brain, specifically oscillatory dynamics in language processing; and the recovery of construction processing in aphasic patients must be differently affected by combinatorial and storage-related properties.

2. Study 1: Electrophysiological investigation of construction processing in the healthy human brain

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2.1 Introduction

The human brain sets itself apart by its great ability to store a huge vocabulary of coherent pieces of information and by its capacity to combine these stored units flexibly to yield virtually endless sets of possible sequences. Such stored units and sequences are manifest in different domains, including those of overt body actions (e.g., reach and grasp) and of meaningful linguistic symbols (i.e., words functioning as parts of subject and predicate; Jackendoff, 2011; Rizzolatti & Arbib, 1998). An action sequence or symbol string is therefore held together by two fundamentally different mechanisms, respectively underpinning the retrieval of stored elements (i.e., basic action schemas; morphemes and words) and the combination of these elements. In linguistics, the traditional separation between a "lexicon" and a "grammar"/"morphosyntax" aims at capturing this important distinction, however with the obvious limitation that combinatorial mechanisms are at work even within "lexical" items (especially morphological and phonotactic rules) and a relevant subset of complex multiword utterances can be seen as stored, unitary whole forms (Goldberg & Jackendoff, 2004; Langacker, 2008). Pinker's "words and rules" framework takes this fact into account (Pinker, 1997), and in the construction grammar framework, a related distinction is sometimes offered between whole-form-stored unitary constructions, including whole idioms as well as elementary meaningful units, such as single words and even morphemes, and more flexible combinatorial schemas, for example, specific argument structure constructions (such as the "double object construction"; Goldberg, 2006). As the lexicon versus morphosyntax division lacks precision when it comes to the mechanisms of symbol retrieval versus combination, the latter distinction is preferred in this work. These terms can also cover the analogous mechanisms of action schema retrieval and combination in the domain of general action (Jackendoff, 2007, 2011; Pulvermüller, 2014; Pulvermüller & Fadiga, 2010).

Because of their fundamental role in human language and action, a main strand of current cognitive and brain research focuses on the theoretical and experimental study of the retrieval of stored meaningful symbols (i.e., lexicosemantic units) and their combination. In much current work, this has led to investigations comparing the processing of words to that of meaningless novel "pseudowords" and that of grammatically correct against incorrect strings.

Because language comprehension is a rapid process and symbol/lexical access and combinatorial/syntactic processes are extremely fast and emerge in close temporal succession, if not in parallel, precise measurement techniques are required to pin down their relative time course. Fortunately, a range of brain correlates exists that seem to distinguish lexicosemantic access and combinatorial morphosyntactic processing.

ERP research on stored symbol retrieval

Access to stored lexical items was first found to be reflected in the N400 ERP/F, whose earliest precursors sometimes yield significant neurophysiological responses already as early as at 250 msec after the onset of written meaningful words versus meaningless pseudowords. Meaningful familiar spoken and written words elicit smaller N400 responses compared with meaningless pseudowords (Holcomb & Neville, 1990), and the familiarity or "lexical frequency" of words is also inversely correlated with N400 size (Kutas & Federmeier, 2011). Earlier (<200 msec) effects of lexical access had been discovered outside the language modality, especially in face processing (Bentin et al., 1996; Schweinberger et al., 2002), and linguistic studies confirmed consistent neurophysiological differences between words and pseudowords (Dien, 2009; Hinojosa, Martí, et al., 2001; Hinojosa, Martin-Loeches, et al., 2001; Pulvermüller, Kujala, et al., 2001; Rudell, 1991), between low- and high-frequency words (Hauk & Pulvermüller, 2004; Sereno et al., 1998), and between words of different linguistic and semantic types (Kiefer, Sim, Herrnberger, Grothe, & Hoenig, 2008; Pulvermüller, Lutzenberger, & Birbaumer, 1995; Pulvermüller, Shtyrov, & Ilmoniemi, 2005; Shtyrov, Butorina, Nikolaeva, & Stroganova, 2014). These results provide strong evidence for early, "pre-N400," brain responses reflecting stored form access and meaning processing (Dien, 2009; Pulvermüller et al., 2009). It has been suggested that the absence of early-latency indices of lexicosemantic (and morphosyntactic) processing in some previous studies may, in part, be related to the fact that sentences and critical words substantially vary with regard to their physical and psycholinguistic properties and to their word recognition dynamics in the spoken language modality, so that the unavoidable jitter in the brain responses brought about by such variance in the stimuli cancels short-lived, early, and focal responses, but not late long-lasting and widely distributed ones (Penolazzi et al., 2007).

ERP research on combinatorial processing

An early ERP, emerging as early as 80–200 msec after appearance of the critical word, indicates whether this critical word fits into its syntactic sentence context or not (Deutsch & Bentin, 2001; Friederici et al., 1996; Hasting & Kotz, 2008; Neville et al., 1991; Pulvermüller & Shtyrov, 2003; Shtyrov et al., 2003). This ERP, first called the "N125," was later relabeled to "early left anterior negativity" (ELAN) to highlight its earliness and the fact that its cortical topography typically shows a maximum at left anterior recording electrodes. This early response was first found to reflect violations of "phrase structure rules," for example, in sentences such as "The man admired Don's *of sketch the landscape" (Neville et al., 1991) or "*Das Eis wurde *im gegessen*" ("The ice cream was *in-the eaten"; Hahne & Friederici, 2002), and is considered to be related to a similar, slightly later response, the "left anterior negativity" (LAN; 300–500 msec), which shows a broader sensitivity to various types of syntactic violations ("The plane took *we to paradise and back"; Coulson et al., 1998). The ELAN emerges in the same time window as the N400, known to reflect semantic combinatorial violations ("He drinks his tea with sugar and *socks"; Kutas & Hillyard, 1984). At even longer latencies (500–700 msec), both syntactic and semantic combinatorial violations seem to be reflected in the P600 response (Gunter et al., 2000). It is in this late interval that the first interaction effects between semantic and syntactic processing indicators have frequently been reported ("*Das Gewitter wurde im *gebügelt*"–"The thunderstorm was in *ironed"; Friederici, 2002), thus motivating the postulate that syntax is processed in a modular fashion first and only later interacts with meaning processing (see, e.g., Friederici, 2002; Gunter et al., 2000). Furthermore, the presence of an early syntactic effect (ELAN) and concomitant absence of a semantic N400 in case of double syntactic–semantic violations was interpreted as further support for serial–modular models of sentence processing (Friederici, 2002).

However, other researchers have found syntax–semantics interaction effects earlier than this, in the N400 time range (Guajardo & Wicha, 2014; Hagoort, 2003; Palolahti et al., 2005). The neurocognitive argument about serial and modular "syntax-first" processing is further complicated by recent methodological concerns regarding the ELAN response, which may arguably be an artefact of spill-over and offset effects from context (Steinhauer & Drury, 2012), thus calling into question the main syntactic index preceding the (semantic) N400 and (syntactic) LAN. On the other hand, the late effects (including both P600 and N400/LAN), for which there is strong evidence across studies, are in danger of reflecting not the first symbol access and combinatorial processes but rather the secondary, potentially epiphenomenal late processes following the understanding of linguistic symbols and their context. Much psycholinguistic evidence supports early, almost instantaneous word comprehension and context integration (Marslen-Wilson & Tyler, 1975), and in single word comprehension, participants can already reliably press buttons to express semantic decisions at 400-msec latency, thus proving that brain responses at this latency occur at a postunderstanding stage (Hauk et al., 2012). Therefore, it is not clear whether brain indices of syntax and semantics at 400 msec and later can speak directly to the question of whole-form access and combinatorial processing.

Evidence for early effects of linguistic symbol access and combination: MMN research

To investigate the earliest brain manifestations of stored form access and combination, as well as their relative time course and potential interaction, it is advantageous to use a brain response that has a history of successfully revealing early cognitive processes. The MMN (Naatanen et al., 2007) has demonstrated this capability, showing sensitivity to differences between words and pseudowords, as well as well- and ill-formed word combinations (Pulvermüller & Shtyrov, 2006). For recording the MMN, word strings are typically presented as rare "deviant" stimuli against a background of frequently repeated "standard" stimuli. The deviants, but not the standards, elicit the MMN, whose amplitude and distribution reflect a range of stimulus features in addition to the perceived acoustic differences between standard and deviant stimuli and, importantly, the status of the deviants as familiar elements matching a memory representation (Naatanen et al., 2007). It is important for the present context that the MMNs elicited by linguistic symbols differ in size (and sometimes polarity and distribution) between words and pseudowords (Frangos, Ritter, & Friedman, 2005; Korpilahti et al., 2001; Pettigrew et al., 2004; Pulvermüller, Kujala, et al., 2001) and equally between linguistic symbols placed in syntactic and ungrammatical contexts (Hanna, Mejias, Schelstraete, Pulvermuller, et al., 2014; Hanna, Shtyrov, Williams, & Pulvermuller, 2016; Hasting et al., 2007; Pulvermüller & Assadollahi, 2007; Pulvermüller & Shtyrov, 2003; Pulvermüller et al., 2008; Shtyrov et al., 2003). Crucially, these MMN responses reflecting symbol storage and combination occur at similar early latencies, ca. 50–250 msec after the input signals first allow for unique stimulus identification. This finding suggests early access both to stored linguistic representations and to the rules flexibly combining them. No study, however, has yet attempted to test both phenomena in a single experiment, and therefore, a simultaneous investigation of storage- and combination-related effects in the same subjects is desirable. Notably, because of meticulous methodological precision borrowed from the tradition of psychophysical research (Carlyon, 2004) — in particular the use of orthogonal designs controlling for the influence of both context and critical MMN-eliciting stimuli — previously reported early "syntactic" and "lexical" MMN effects are not subject to concerns that have been raised against the ELAN and other very early language-related ERP components (see discussion above, "*ERP research on combinatorial processing*", and Section 1.). MMN paradigms even allow the use of identical recordings of syllables for eliciting brain responses to well- and ill-combined strings. For example, Pulvermüller et al. (2001) used the critical syllables "kko"[2] and "kku" presented, respectively, in the contexts of the syllables "pa" and "ta," where they complete meaningful words, and the reverse combinations "pa-kku" and "ta-kko," which are Finnish pseudowords, and found larger MMNs in meaningful word contexts. This orthogonality of context and critical stimuli to the investigated factor rules out issues previously claimed to confound traditional language responses, such as offset, context, and physical features of the critical stimuli. A further advantage of the MMN (apart from its earliness) is that it can be elicited without participants paying active attention to language stimuli or performing an overt task

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[2] Double letters are used to indicate geminate consonants.

such as judgment of grammaticality or meaningfulness. Such tasks have frequently been applied when N400 and P600 responses were elicited, and it is therefore unclear to which degree these late components reflect task strategy-related processes or stored symbol and combinatorial processing per se. In contrast, paradigms where participants are distracted from linguistic stimuli elicit linguistic MMNs indexing stored symbol retrieval and combination may allow for conclusions on automatic language processes, or at least on processes that are independent from the participants' active attention to verbal materials. On the negative side, MMN designs require frequent repetitions of (the same or very similar) critical deviant stimuli (and even more frequently occurring standards), thus leading to a somewhat artificially repetitive use of language, which carries a risk that differences normally present in everyday language processing may fall victim to repetition effects. However, given that previous MMN paradigms yielded reliable and reproducible early linguistic effects and concordant results have been reported with more variable but still precisely controlled paradigms (MacGregor et al., 2012; Pulvermüller & Shtyrov, 2006), it appears to be a fruitful strategy to use this component for probing the earliest brain indices of linguistic symbol retrieval, combination, and the interaction of these factors. In addition, it cannot be denied that, to a degree, repetitive and "artificial" paradigms have paved the way to a better understanding of a range of cognitive processes, including memory (Fuster, 2015), attention (Mangun, 1995; Naatanen et al., 2007) and prediction (Schultz, 2008), and it is therefore not impossible that useful information can be obtained from such paradigms in the language domain as well.

Overview of the present study

Here, it was used a variant of the classic oddball paradigm optimised to minimize the duration of complex experiments, the so-called "optimal" or "multifeature" paradigm (Näätänen, Pakarinen, Rinne, & Takegata, 2004; Pakarinen et al., 2009), to record deviant stimulus responses and MMNs to word and pseudoword/-morpheme combinations, which were either (1) well-formed phrases (such as "I jump") or they included (2) a not-stored (or "unstored") pseudoword and -morpheme ("I junt*"), (3) a combinatorial violation of syntactic agreement ("*He jump"), or (4) both ("*He junt*"; see also Table 1). In contrast to previous studies, a fully orthogonal design was adopted, in which the same critical syllables appeared equally frequently in all four conditions, and all the items building up the contexts were also exactly balanced between conditions (see Table 1; Figure 1). On the basis of pre-existing work, early neurophysiological differences following critical syllable onset were expected, with 50–250 msec latency between well-formed and unstored stimuli ("lexical" effect) and between well-formed and ill-combined strings ("morphosyntactic" effect). A serial modular-type model would predict interaction effects between storage and combination only at a longer latency, significantly later than the early storage-related and combinatorial effects, whereas simultaneous access and interactive processing accounts suggest a simultaneous interaction effect and divergence between well-formed, single-violation, and double violation conditions early-on.

2.2 Materials and Methods

Participants

Twenty-four (15 women; average age = 22.7 years, range = 19–35 years) right-handed (average laterality quotient = 87.4, range = 50–100, SE = 3.1; Oldfield, 1971) monolingual German native speakers with no history of neurological or psychiatric disease, normal hearing, and normal or corrected-to-normal vision participated in this study. Data from 17 participants (10 women; average age = 22.9 years, range = 19–35 years; average laterality quotient = 89, range = 50–100, SE = 3.4) were included in the final analysis (see EEG Data Processing). All participants gave written informed consent and were paid for their participation. The study was approved by the ethics committee of the Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, and was conducted in compliance with the principles of human research.

Stimuli

As stimuli, 16 short sentences were used, each consisting of a German pronouns, *ich* (meaning *I*) or *wir* (*we*), followed by one of four inflected German verbs, overtly marked either by the suffix *-e* for first person singular,[3] *leide*, *zeige* (*suffer*, *show*), or by the suffix *-en* for first person plural, *schweigen*, and *scheiden* (*keep silent*, *separate*), or by one of four phonotactically legal pseudowords consisting of the same inflectional suffixes attached to a meaningless "pseudomorpheme" not part of the German lexicon, *leigen**, *schweide**, *zeiden**, *scheige** (see also English examples in the Introduction, study overview section). These stimuli were chosen because, in typical pronunciation, the acoustic information about the voiced stop consonant in the middle of each word/pseudoword and the information about its inflectional suffix, which was either an [ə] or the [n] (to which the unvoiced syllable [ən] reduces in informal and fast discourse), become available at the same time. Note that, because of coarticulation effects, it is the earliest part of the formant transitions at the start of the last syllable that discloses both the identity of the stop consonant crucial for identifying the verb stem and that of the immediately adjacent and overlapping voiced vowel or nasal consonant critical for recognizing the inflectional affix. Therefore, this kind of words and pseudowords—with amalgamated stop consonant and adjacent minimal affix—offers a unique opportunity to study the brain responses to strings in which stored verb stems are contrasted with unstored pseudomorphemes whereas combinatorially regular miniconstructions (i.e., syntactically correct short sentences) are contrasted with morphosyntactically ill-formed strings containing agreement violations.

To avoid coarticulation effects between syllables that could reveal information about the identity of the word final syllable already during the word-initial one, all bisyllabic words and pseudomorphemes were produced by cross-splicing and combining syllables spoken in isolation. Multiple repetitions of the two pronouns and of the eight syllables *lei*, *schwei*, *zei*, *lei*, *de*, *gen*, *ge*, and *den*, each spoken in isolation by a female native German speaker, were recorded; among these, only one token of each pronoun and syllable was selected. The syllables *gen* and *den* were pronounced in reduced form, as [gn] and [dn], as it is usual in connected speech, where the "schwa" sound [ə], which may appear in-between the consonants, is frequently omitted.

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[3] The *-en* suffix can also mark third person plural and infinitives in German, and the *-e* suffix can also index imperative; however, the context of first person pronouns biases their parsing toward the first person understanding

Isochronous perception of rhythmic speech is not related to regularity of the interval between syllable onsets, but to regularity of occurrence of a perceptual property immanent to syllable structure, the so-called “perceptual center” or p-center (Allen, 1972; Morton, Marcus, & Frankish, 1976). For this reason, and to match the rhythmic structure between stimulus constructions, the first syllables of every (pseudo)verb were aligned according to the largest change in acoustic energy identifiable in the sound envelope; this resulted in a regular beat and isochronous presentation of stimulus phrases. A similar adjustment relative to the p-center was chosen for the first syllable of the phrase, that is, the pronoun, although the same pronoun was used throughout each block of the experiment. The phrase-final syllables were aligned by onset as their onsets and rising flanks of their acoustic envelopes were similar, so that no break in perceived rhythms was caused. Careful stimulus selection and slight adjustment using Adobe Audition CS5.5 software (Adobe Systems Inc., San Jose, CA) ascertained that corresponding items were matched pairwise for length (*ich-wir* were 365 msec long, *lei-schwei* 310 msec after p-center, *schei-zei* 366 msec after p-center, *de-gen* 275 msec, *den-ge* 230 msec), average sound pressure level, and fundamental frequency (F0). The matching for the first syllables in the (pseudo)verbs was relative to the p-center (see Figure 2.1).

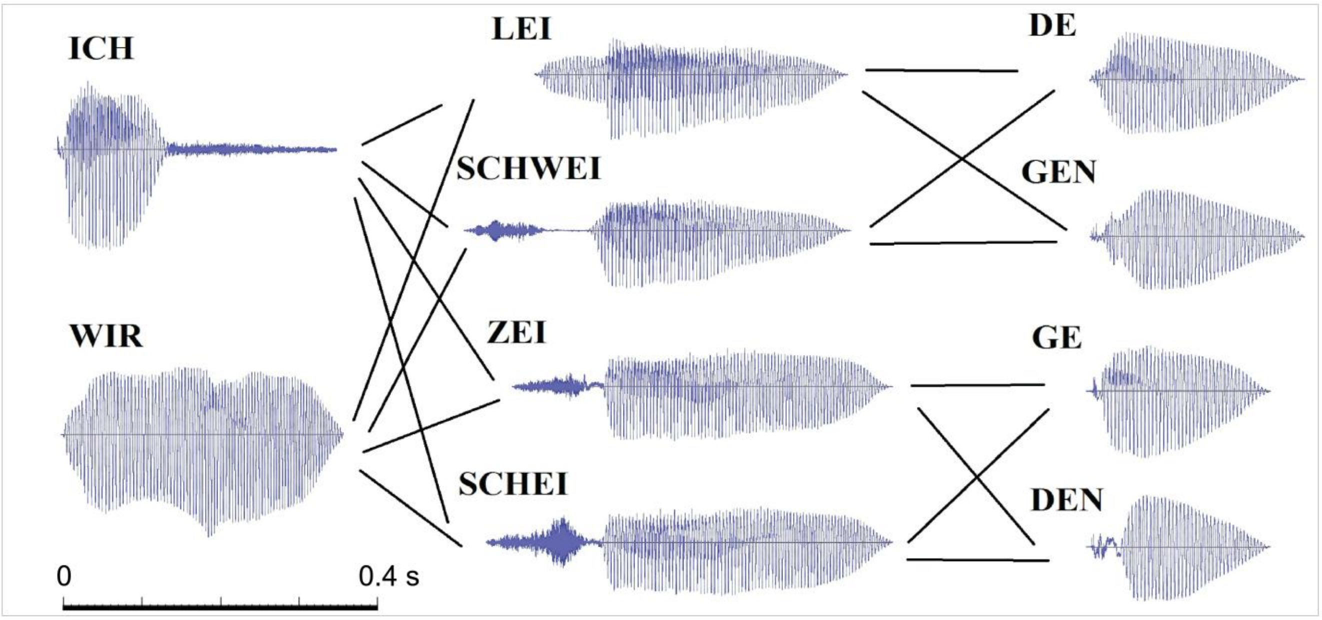

Figure 2.1. Stimulus waveforms and schematic of possible combinations of pronouns and syllables matched pairwise for length, average sound pressure and fundamental frequency. For further explanation and illustration, see section 2.1 Material and Methods and Table 2.1.

Experimental design

In a fully balanced orthogonal design, 16 phrases each including a pronoun and an inflected verb varied in their combinatorial (well- vs. ill-combined) and storage-related (stored vs. unstored) status, resulting in the four conditions (see Table 2.1), indicated here as the "well-formed," "unstored," "ill-combined," and "double violation" conditions.

	Stimuli	**Storage**	**Combination**
Well-formed	ich lei**de (I suffer)**, ich zei**ge (I show)**, wir schwei**gen (we keep silent)**, wir schei**den (we separate)**	+	+
Unstored	ich schwei**de***, ich schei**ge***, wir lei**gen***, wir zei**den***	-	+
Ill-combined	*wir lei**de**, *wir zei**ge,** *ich schwei**gen**, *ich schei**den**	+	-
Double violation	*wir schwei**de**, *wir schei**ge*,** *ich lei**gen***, *ich zei**den***	-	-

Table 2.1. Overview of design, conditions, and stimuli. The stimuli were mini-constructions consisting of three syllables each: a pronoun, followed by a verb-initial syllable, and finally a verb-final syllable. The verb-final syllable was the 'critical stimulus' (given in bold face), which, at the same point in time, disambiguated and specified the verb stem (or not-stored pseudo-stem) and the agreement of the verb-final inflectional affix (or combinatorial "ill-formedness"). Analogous English examples are provided in the Introduction.

Each of the four conditions included all first words (pronouns) and first and second syllables of the second word in a balanced fashion so that any acoustic, physical, and psycholinguistic differences between contexts or critical syllables could not explain between-condition differences. In particular, the four construction-final syllables *de*, *gen*, *ge*, and *den*, to which neurophysiological responses were analysed, appeared in each of the four conditions the same number of times. Therefore, the four condition and stimulus types varied with regard to the features [+/− symbolically stored] and [+/− regularly combined], that is, in their morphosyntactic agreement between the personal pronoun and the inflectional suffix (factor Combination) and in their inclusion of lexical elements (factor Storage), but not with regard to critical or context stimulus materials. As the voiced stop consonants [d] and [g] orthogonally distinguished stem morphemes from pseudomorphemes, the use of two different inflectional suffixes, [ə] and [n], equally contributed to defining combinatorial acceptability.

Experimental setup

Each of the 16 two-word miniconstructions was presented 80 times during the experiment to allow for the calculation of ERPs with high SNRs. Each pronoun was considered a standard stimulus and the inflected verb or pseudoverb a deviant stimulus of a multifeature MMN design (Näätänen et al., 2004; Pakarinen et al., 2009). There were two blocks, each with one of the pronouns as standard stimulus. After each standard stimulus, one of the eight deviant words or pseudowords followed in random order. The stimulus onset asynchrony (SOA) between subsequent standard and deviant stimulus words was ca. 650 msec. To ascertain that a constant rhythm was perceived by participants, standard and deviant words were timed relative to the p-center of their first syllable (see explanation in the "Stimuli" section above). The onset of the word and phrase disambiguating final syllable followed 650 msec upon the p-center of the deviant stimulus word's first syllable. Note that all ERPs were measured relative to the onset of the critical syllables [də], [gə], [dn], and [gn]. The delay was therefore 650 msec between syllable p-centers. The SOA of subsequent trials was 1950 msec. Blocks lasted 20 min each, and block order was counterbalanced across participants; the sequence of stimuli in each block was pseudorandomized, not allowing direct succession of two copies of the same deviant.

Stimuli were presented through headphones at a comfortable hearing level. Participants were seated in a dimly lit, electrically shielded, and acoustically isolated chamber. They watched a silent movie throughout the duration of the experiment and were instructed to ignore the acoustic stimuli and focus their attention on the movie.

EEG recording

The EEG was recorded (0.1–250 Hz band pass, 1000 Hz sampling rate) through a 128-channel EEG setup (BrainProducts, Gilching, Germany) using active electrodes mounted in an extended 10–05 system specific cap and a reference electrode on the tip of the nose of the participant. Three electrodes were mounted at the left supraorbital and infraorbital margins and the right outer canthus, respectively, to record the horizontal and vertical EOG.

EEG data processing

Data were down-sampled offline to 200 Hz. Signals from EOG electrodes were converted offline to bipolar vertical and horizontal EOG signals. Channels containing no signal or substantial artifacts were rejected after visual inspection in 9 of the 24 subjects (between one and seven channels per subject). Subsequently, an offline 30 Hz lowpass filter was applied. Epochs time-locked to critical, construction final, syllable onset (time 0), starting 100 msec before and ending 600 msec after it, were then obtained. Independent component analysis was performed on zero-mean epoched data, decomposing them into 35 components. Components correlating with the EOG signal ($r \geq .3$ or $r \leq -.3$) were rejected (Groppe, Makeig, & Kutas, 2009; Hanna, Mejias, et al., 2014b; Hanna & Pulvermüller, 2014). An additional analysis was run with a threshold of $r \leq \pm.5$, and producing very similar results. Those bad EEG channels that had been rejected were then spherically interpolated. The processing steps to this point were carried out with the EEGLAB 11.5.4b suite (Delorme & Makeig, 2004) in Matlab R2012b programming environment (The MathWorks, Natick, MA).

The following steps were carried out in the SPM8 suite (Litvak, Mattout, Kiebel, Phillips, Henson, Kilner, Barnes, Oostenveld, Daunizeau, Flandin, et al., 2011) for Matlab R2012b. The mean voltage value in the interval from −100 to 0 was subtracted from the whole epoch. Epochs with voltage variation of ±80 μV from 0 were then rejected, and only subjects with a rejection rate below 20% (Lopez-Calderon & Luck, 2014; Luck, 2014) were included in the final analysis ($n = 17$). The reason for the rejection of four data sets lay in poor quality of the recordings (because of line noise on signals and/or too low impedances during the recordings); three further rejections were due to excessive blink rates. The average trial rejection rate of the remaining 17 data sets included in the final analysis was ca. 6% with an even distribution across conditions. ERPs to the critical deviant stimuli (final syllables) were then obtained averaging trials over each condition for each subject. The ERP to the standard was obtained by averaging together all the trials in response to both standard stimuli. The MMNs were obtained by subtracting the averaged standard response from the ERPs to the critical syllable of each the four deviant conditions. Both the deviant responses and the MMNs were used for statistical analysis.

Statistical analysis

All statistical analyses were performed using Statistica 12 software (Statsoft, Tulsa, OK). To target the well-known fronto-central maximum of auditory and speech-evoked ERP components (Kutas & Federmeier, 2011; Näätänen, 1990; Pulvermüller & Shtyrov, 2006), 13 left fronto-central electrodes (AF3, AFF1h, AFF5h, F3, F1, F5, FFC1h, FFC3h, FFC5h, FC1, FC3, FCC1h, FCC3h) and the 13 homotopic ones on the right were chosen. Additional analyses were performed also including the midline electrodes, which confirmed the reported results unless mentioned otherwise. To estimate the time course of neurophysiological activity elicited by the critical syllable stimuli the root mean square (RMS) of the grand-averaged ERP signal across these channels and across all deviant conditions was calculated (Figure 2.2). The RMS showed one large early deflection (ca. 50–250 msec) and one smaller and later one (ca 300–500 msec). The early time window for analysis (70–210 msec) was identified as the time range comprising 70% of the area under the largest deflection of the RMS curve. As a double peak emerged in this early time window (see Figure 2), this window was divided into two halves to allow for more fine-grained temporal analysis. A second analysis was performed on the conventional N400 window, 300–500 msec; also this second window was split into smaller parts, in this case of 50 msec width each, for fine-grained temporal analysis. Average voltage values were calculated for each time window, hemisphere, and condition for each subject and submitted to two separate repeated-measures ANOVAs with the factors Time (2 or 4 levels) × Laterality (2) × Combination (2) × Storage (2). Significant interactions were further investigated using post hoc comparisons with the Bonferroni-corrected least significant difference t statistic, which is justified in case of absence of sphericity violations in the results

(Hsu, 1996; Mitzel & Games, 1981; Scheirs, 1992). ANOVAs were carried out on both deviant responses and on MMN responses.

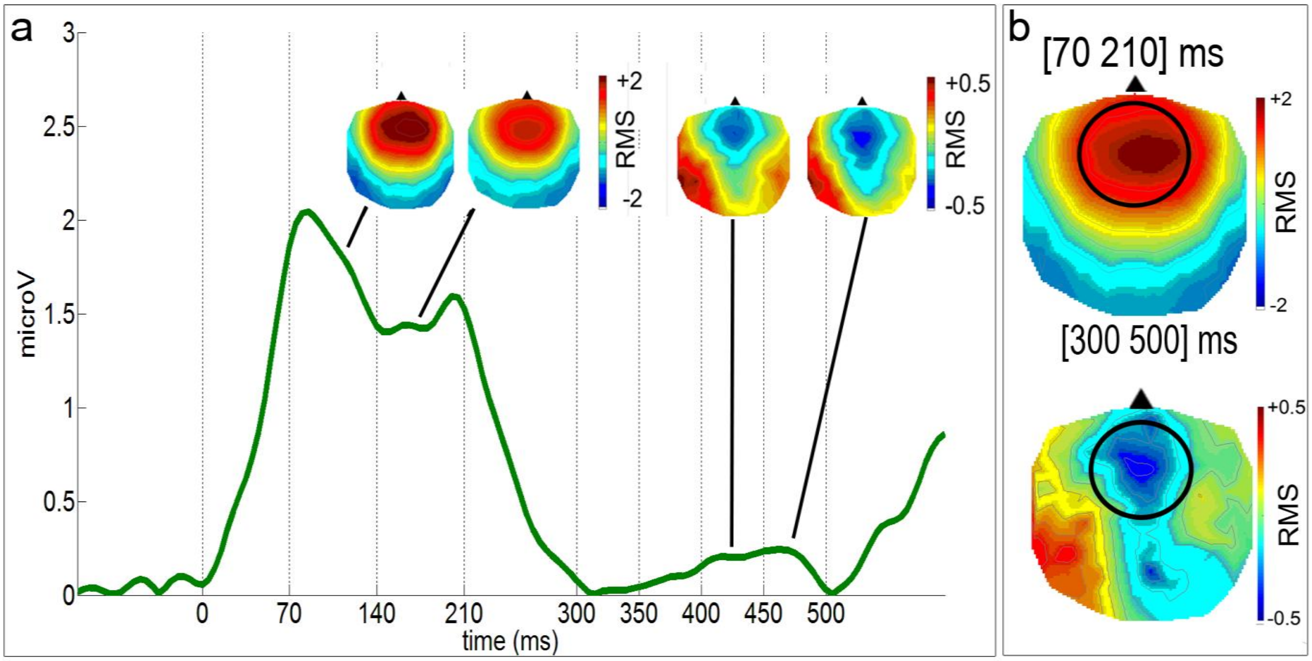

Figure 2.2. Time course of the brain response (RMS across all conditions) elicited by the critical deviant stimulus syllables. a) RMS responses calculated across fronto-central electrodes, with correspondent average scalp distributions for the intervals of highest activity. Analysis time windows are indicated. b) Scalp distributions for the two time intervals of major activity showing the localization of the fronto-central electrodes used for statistical analysis (black circle).

2.3 Results

Early time window

As Figure 3A shows, a positive fronto-central ERP component dominated the time interval from ca. 50 to 250 msec, which was elicited by the construction-final syllable. This early positivity corresponded to the RMS response in the same time window (Figure 2.2), whose double peak was well captured by the time window between 70 and 210 msec. A similar positive ERP was elicited by the standard stimuli. The subtraction of the standard response from the deviant responses yielded MMNs for all four conditions, which were also comprised in the 70–210 msec time windows (Figure 2.3B). Whereas the positivity elicited by the critical deviant stimuli (final syllables) showed a symmetrical fronto-central topography, the ERP to the standard was right-lateralised (Figure 2.3A) and thus the MMN topography was right lateralised. Within the first half (70–140) of the early time window (70–210 msec), deviant ERPs and MMNs to well-formed constructions tended to be less positive- and more negative-going than those to both single violation conditions and double violations. In the second half (140–210 msec), the double violation condition appeared to elicit a more positive-going (less negative) response than all other conditions.

Statistical analysis on ERPs confirmed significant early differences between conditions. A significant interaction effect of the factors Time, Storage, and Combination (F(1, 16) = 6.59, p = .02, ηp2 = 0.29; Figure 2.4A) showed a non-additive influence of these factors in the 70–210 window. The Bonferroni test (corrected for 16 comparisons) confirmed that the response to the well-formed stimuli was significantly different (more negative-going) from the ones to the unstored (p = .018) and double violation (p = .006) conditions in the first half (70–140 msec) of the early time window. In contrast, the second half-window (140–210 msec) showed less negative-going ERPs to the double violation condition as compared with those to well-formed (p< .001), unstored (p=.008) and ill-combined (p=.02) strings (Figure 2.4A and B). Comparing condition-specific differences in ERP amplitudes between the first and second halves of the early window revealed a significant increase only for the single-violation conditions (unstored: p < .001; ill-combined: p = .004; see Figure 2.4A). From the same analysis emerged a significant interaction of Time and Laterality (F(1, 16) = 6.24, p = .023, ηp2 = 0.28). Repeating the same analysis without the Laterality factor and including the midline electrodes confirmed the interaction of Time, Storage, and Combination.

MMN responses obtained by subtracting ERPs to the standard stimuli from the critical deviant syllable ERPs confirmed the Time × Storage × Combination interaction, resulting in the same statistical results as the deviant ERP analysis (F(1, 16) = 6.59, p = .02, ηp2 = 0.29), because the same standard response had been subtracted from all four deviant conditions. Post hoc tests also confirmed the differences revealed by the deviant responses. Likewise, the interaction of the factors Time and Laterality was confirmed (F(1, 16) = 6.24, p = .023, ηp2 = 0.28), and a significant main effect of Time (F(1, 16) = 24.9, p < .001, ηp2 = 0.6) emerged because of larger MMNs in the second subwindow. Note that the Time × Storage × Combination and the Time × Laterality interactions were present in the deviant responses already; therefore, these interaction effects can be attributed to the deviant responses.

Late time window

The positive deflection elicited by the critical deviant syllables was followed by a negative ERP ranging from ca. 300 to 500 msec (Figure 2.3A), which corresponded to the second deflection of the RMS curve (Figure 2.2). In this time range typical for the N400, single violation conditions tended to show more “less positive-”/more negative-going ERPs/MMN. However, the ANOVA performed on the data from the late interval following the critical construction final syllable did not confirm any between-condition differences.

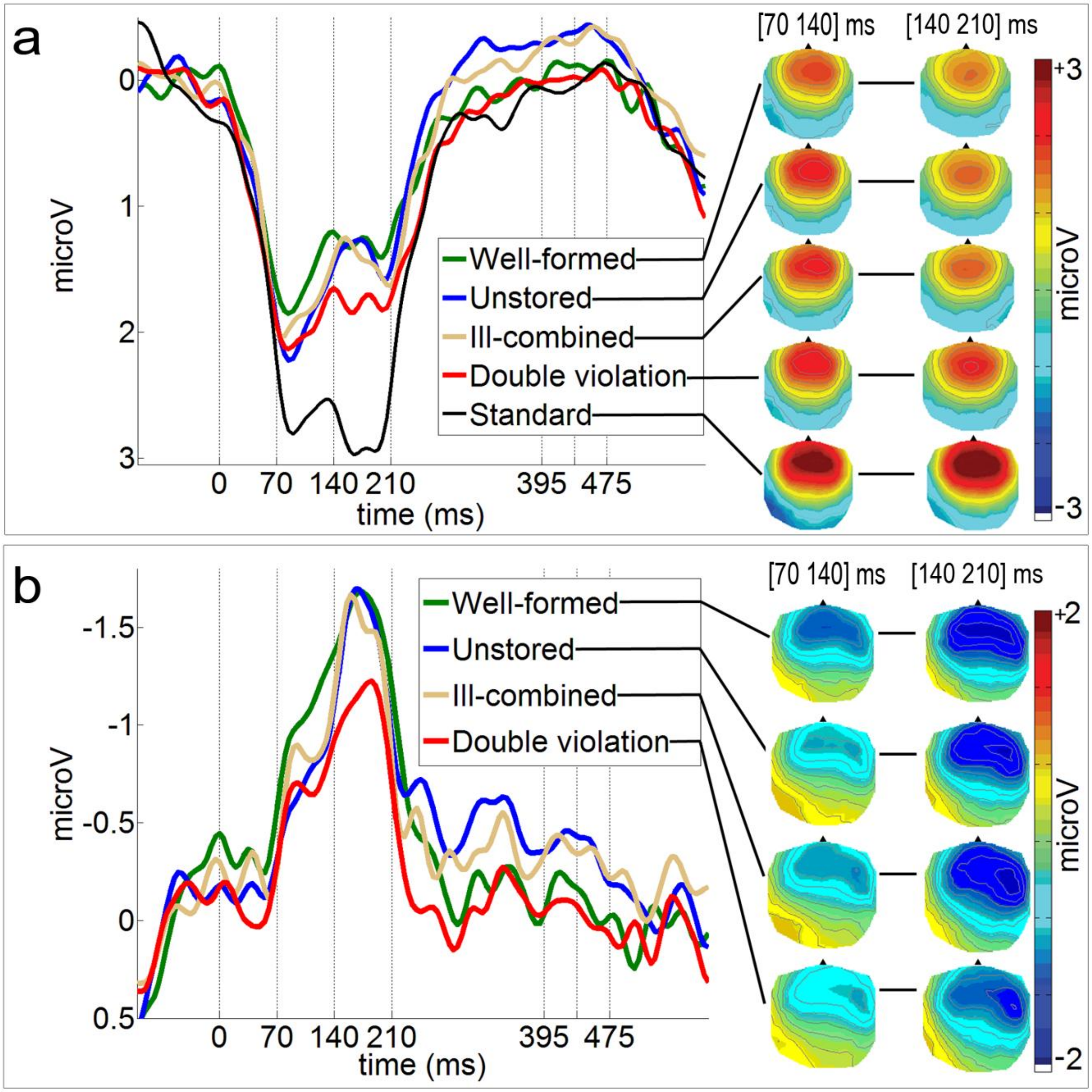

Figure 2.3. a) Electric brain responses in µV to the critical deviant and standard stimuli averaged across the 26 fronto-central electrodes. The grand average ERPs for all four critical deviant stimuli of the four conditions and to the standard stimulus ERP are presented separately. Analysis time windows are indicated. Topographies for each major time interval and condition are displayed on the right. Note the divergence between constructions including words vs. the other conditions between 70 and 140 ms and the divergence between "double violation" condition and the rest at 140-210 ms. b) MMN responses resulting from the subtraction of the standard response from each critical deviant ERP. Topographies for each major time interval and condition are displayed on the right.

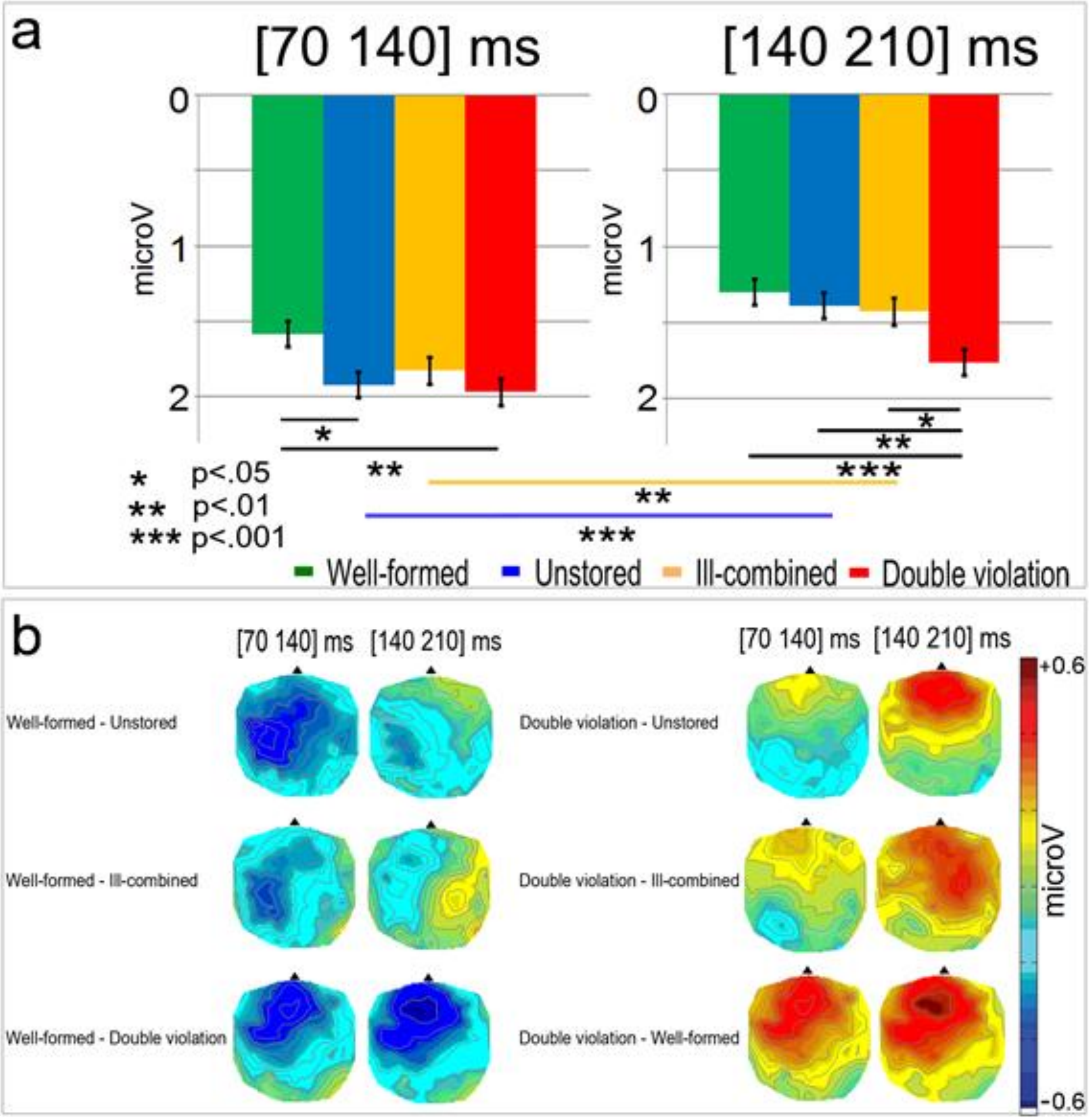

Figure 2.4. Interaction of storage and combination over the two halves of the early time window (140-210 ms) as indicated by the statistically significant Time x Storage x Combination interaction. a) Bar graph displaying the interaction. B) MMN/ERP topographies referenced to the well-formed condition (left columns) and to the double-violation condition (right columns). In the first half of the early time window, the well-formed construction seems to separate from all 3 violation conditions, whereas in the second half, the double violation condition is neurophysiologically distinct from the rest.

2.4 Discussion

In an orthogonal design balancing out any additive effects of the contexts and the critical disambiguating syllables, early MMN brain responses indexed processing differences between stored words versus “unstored” pseudowords, and, crucially, an interaction effect of storage- and combinatorially related properties. This interaction between Storage and Combination emerged between 70 and 210 msec after critical disambiguating syllable onset, where MMNs to well-formed phrases were larger than those to double violation strings, but unstored and asyntactic “single violation” conditions produced initially small MMNs, which significantly increased over time and paralleled those of well-formed phrases toward the end of the early time window. The differential dynamics across the four conditions were manifest in a significant interaction of the factors Storage, Combination, and Time. These results indicate that the brain computes combinatorially flexible parts of constructions and whole form-stored ones at similarly early latencies and within (one or more) interactive system(s). Phrased in more traditional terms, the results suggest that “lexical/symbol access” and “syntactic rule application” run in parallel, interacting with each other within the first ca. 200 msec after the onset of the disambiguating syllable. An anterior negativity dominating the time interval around 400 msec failed to reveal significant differences between conditions in the present “non-attend” task. The early interaction involving Storage and Combination factors may raise questions about psycholinguistic models claiming that modular syntax processing emerges first and interacts with other mechanisms only later. Below, the present results are explained and discussed in context of previous research in the neurophysiology of language, also highlighting their potential implications for linguistic and brain theory.

Relationship to pre-existing research

This study employed a relatively new method for recording the MMN brain response, the so-called “optimal” or “multifeature” paradigm (Näätänen et al., 2004; Pakarinen et al., 2009). This paradigm is similar to a classic oddball experiment but allows investigation of brain responses to a range of deviant stimuli in one block, saving substantial time, especially if several different conditions (like the 16 different constructions in the present study) are in the focus. A number of previous language studies successfully used the multifeature paradigm to investigate early brain correlates of linguistic processes (Cappelle et al., 2010; Garagnani, Shtyrov, et al., 2009; Shtyrov, Kujala, et al., 2010). In the present setup, pronouns were used as standard stimuli alternating with deviant verb stimuli whose final and critical syllables simultaneously revealed information about the lexical status of the final word or pseudoword and its combinatorial syntactic agreement with the context pronoun. This information became manifest neurophysiologically in the first 210 msec after critical syllable onset.

Pre-existing work had already shown neurophysiological dissociations between stored meaningful words and not-stored meaningless pseudowords at early latencies using a range of different brain responses (Dien, 2009; Hanna & Pulvermüller, 2014; Hinojosa, Martí, Munoz, Casado, & Pozo, 2004; Hinojosa, Martin-Loeches, et al., 2001; MacGregor et al., 2012; Pulvermüller, Kujala, et al., 2001; Shtyrov & Pulvermüller, 2002). The latencies at which these “lexical” or storage-related effects occurred varied to a degree across study, ranging from “early” (150–200 msec; Pulvermüller, Kujala, et al., 2001) to “ultraearly” (even around 50 msec; MacGregor et al., 2012), but all of these effects ended to appear before the typical N400 time window of 250–500 msec where lexical and semantic effects have most frequently been reported[4] (Kutas & Federmeier, 2011; Pylkkänen & Marantz, 2003). Similarly, early neurophysiological signs of grammaticality and syntactic violation have been reported in equally early time windows, in the so-called ELAN and syntactic MMN responses (see section 2.1 above and Deutsch & Bentin, 2001; Friederici et al., 1996; Hanna, Mejias, Schelstraete, Pulvermuller, et al., 2014; Hanna, Shtyrov, Williams, & Pulvermuller, 2016; Hasting & Kotz, 2008; Hasting et al., 2007; Neville et al., 1991; Pulvermüller & Assadollahi, 2007; Pulvermüller & Shtyrov, 2003; Pulvermüller et al., 2008; Shtyrov et al., 2003). The earliest of these syntactic responses were seen already within the first 100 msec after critical stimulus

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[4] The latencies in the present study are calculated from the onset of the second, construction-disambiguating syllable but most previous N400 studies on spoken word processing calculated latencies from word onset. Calculated relative to word onset, the present results would have a latency of >600 msec. Note, however, that the first syllable of the phrase-final word did not include any information about lexical status or grammaticality of the constructions. This information was first manifest at the onset of the critical syllable and therefore the proper calculation of latencies should start at this “divergence point.”

onset (Herrmann et al., 2009; Pulvermüller et al., 2008); these combinatorial syntax-related responses were therefore of the same latency as the “ultraearly” lexicality responses related to storage. In the literature on the ELAN—the oldest and most established early syntax response—a range of methodological criticisms have been raised (see sections 1.2, *Cascaded processing*, and 2.1, *ERP research on combinatorial processing*). For example, it was argued that the ELAN may be an artifact of poorly controlled baseline differences or differences in the stimulus-eliciting verbal materials (Steinhauer & Drury, 2012). Notably, the orthogonal designs, in which several of the syntactic MMN responses were recorded (Hanna, Mejias, Schelstraete, Pulvermuller, et al., 2014; Pulvermüller & Shtyrov, 2006; Shtyrov et al., 2003), controlled both context and critical stimulus effects by using the same contexts and critical stimuli in different combinations—the technique also adopted here— thus ruling out any additive context or stimulus effects. Syntactic MMNs consistently appeared substantially earlier than the most commonly investigated index of syntax processing, the P600 (Osterhout, McLaughlin, & Bersick, 1997).

The present study appears to be the first one to find early neurophysiological effects of lexicality and morphosyntax within the same study and the same participants in response to minisentence stimuli. Therefore, these data are consistent with findings about early lexical and syntactic responses. The conclusion suggested (but not proven) by the literature, namely that the early lexical and syntax effects are strictly simultaneous, therefore gains support from the present data set. In a time window between 70 and 210 msec after critical stimulus onset, the brain response reflected the storage-related and combinatorial features of the strings. In addition, these factors interacted with each other, which is consistent with not only simultaneous but also interactive processing of storage-related (including lexical) and combinatorial (including morphosyntactic) information.

Methodological issues

The polarity or the recorded ERPs to standard and deviant stimuli was positive relative to the prestimulus baseline. This may seem unexpected in an MMN experiment, where negative frontocentral ERPs may be expected. However, several auditory MMN studies of linguistic materials using SOAs comparable with those in the present study have previously reported similarly positive deviant and standard responses (Jacobsen, Steinberg, Truckenbrodt, & Jacobsen, 2013; Steinberg, Truckenbrodt, & Jacobsen, 2011; Truckenbrodt, Steinberg, Jacobsen, & Jacobsen, 2014). Such positive shifts of early ERPs seem common when stimulus words are presented close to each other, with only short delays in-between, as it is common in everyday language usage (Shtyrov, 2011).

Statistical analyses were performed on deviant responses and, in a second step, on MMNs calculated from the critical parts of the deviants and the averaged standard responses. Results were the same, as the same values were subtracted from all deviant condition responses, and this was so because all of the conditions examined in this study used the same contexts in a balanced fashion (cf. Table 2.1). However, it should be noted that, for calculating each MMN subtraction, physically different deviant and standard stimuli were used, and therefore, the subtracted MMN responses were affected by the brain correlates of these physical stimulus differences, however, in an additive fashion not affecting the statistics. The topography of the main early brain response (see Figure 3B) was a frontocentral negativity with posterior polarity inversion, approximately at the level of the mastoids, which matched the typical topography of an MMN and thus suggests that a true MMN was recorded. The laterality of the MMN responses was mainly due to right laterality of the subtracted response to standard stimuli (Figure 3A); it will therefore not be interpreted. A further reason for not interpreting the laterality of the MMN in the present context is the absence of any statistically reliable interaction effect of this variable with the factors of interest, Storage and Combination.

Advantages and disadvantages of the MMN paradigm

As mentioned above, the four conditions—“well-formed,” “unstored,” “ill-combined,” and “double violation”—all used the same, physically identical critical syllables and all used the same context syllables (see Figure 2.1; Table 2.1). This multiple orthogonal design (both storage-related and combinatorial features were orthogonalised, see section 2.2, *Experimental* *design*) ruled out the possibility that additive effects of physical differences of contexts or critical syllables could explain any main effects or interactions obtained from the present experiment. Therefore, an attribution of between condition differences to Storage- and Combination-related cognitive processing is justified. The fact that the MMN offers such precise control of stimulus context and features can certainly be seen as an advantage over designs where a range of natural sentences with and without pseudowords and/or syntactic rule violations are presented, but either context, critical stimuli, or both differ between conditions. However, this advantage comes at the price of restricting the investigation to the processing of a small number of stereotypically occurring items, as in the present case of 16 miniconstructions. This limitation of the stimulus space may be seen as unnatural, although, on the other hand, it has a strong tradition in acoustic psychophysics (Carlyon, 2004). Instead of forcefully arguing against such possibly "unnatural" designs, one should rather suggest the possibility that cognitive phenomena otherwise difficult to access properly can be explored using such psychophysically inspired methods. It is certainly possible that a repetitive MMN design abolishes processes normally occurring in language comprehension because of the frequent repetitions; however, positive effects even present under such "boring" repeat conditions cannot easily be ignored and might shed light on the automatic nature of some linguistic processes. In case of the present results, it appears that the early simultaneous effects of stored symbol access, combination, and their possible interaction are phenomena worthy of further exploration. It may be that MMN paradigms, where participants are actively distracted from the incoming sounds and words, are well suited to reveal aspects of automatic language processing that are shared between innovative and stereotypical language use.

Implication for language theories

On first view, the result of a significant interaction between lexical, morphosyntactic, and temporal factors at early latencies (70–210 msec) contradicts predictions of so-called "syntax first" models (see Section 1.2 and Friederici, 2002; Garrett, 1989), which are commonly understood as predicting a primacy of syntax effects compared with most other psycholinguistic processes. However, it is evident that syntax and combinatorial information processing requires phonological and lexical information to operate on, and looking more closely at actual models and their predictions, word form access is typically seen as a processing step preceding syntactic analysis in strictly serial “syntax first” models of language comprehension (Figure 1 in Friederici, 2002). The present, early near-simultaneous lexicality/storage and syntax/combination effects seem consistent with this position. It is noteworthy, however, that syntax effects were seen with subject–verb agreement violation, a type of syntactic process that has been claimed to follow upon earlier stages of “phrase structure building”. The present study confirms earlier observations that syntactic agreement, or lack thereof, is neurophysiologically reflected at the earliest stages of the speech comprehension and combinatorial analysis process (Deutsch & Bentin, 2001; Hasting & Kotz, 2008; Shtyrov et al., 2003) rather than only at later stages. The present results suggest that interactions between syntactic and lexical (or, more precisely, as explained in the Introduction, combinatorial and storage-related) processes occur early-on, a feature difficult to explain in the modular tradition.

Previous studies on the interaction between combinatorial processes of syntactic nature and semantic processing had reported differential responses and interactions around 400 and 600 msec latency, as discussed in the Introduction (Guajardo & Wicha, 2014; Gunter et al., 2000; Hagoort, 2003; Palolahti et al., 2005). The present finding of an interaction between lexicality and syntax (storage vs. combination mechanisms) may be seen as indicating interactive processing very early on. Whether the lexical storage feature monitored by the present MMN paradigm also taps into semantic processing interacting with syntax early-on needs to be addressed by future research.

Rather than being interpreted in terms of lexical and syntactic processing, the present results may reveal interacting brain mechanisms for symbol retrieval and combination. This is a promising strategy, because recent research has shown that many aspects of constructions that have traditionally been described by combinatorial rules may in fact be related to whole forms storage and, vice versa, some aspects of “lexical storage” may be underpinned by combination. For example, there are several reasons to assume that idiomatic constructions (such as “catch some sun”) are, at least in part, whole form-stored although they are open to a description in terms of combinatorial syntactic rules (Langacker, 1991), and there are, without any doubt, multiple combinatorial affixation processes at work in morphology, which produce complex words that may be seen as entries of the lexicon (Marslen-Wilson, Tyler, Waksler, & Older, 1994). As already mentioned in Sections 1.1 and 2.1, these and other facts render the traditional distinction between lexicon and syntax insufficient for capturing the relevant neurocognitive processes. Part of what is traditionally seen as the "lexicon" is not whole form-stored but instead dynamic and combinatorial, whereas some "syntactic strings" are stored as whole form, rather than combined (Goldberg, 2006; Langacker, 1991; Pinker, 1997). The storage/combination distinction therefore appears to discriminate between the relevant fundamental mechanisms, whereas both lexicon and syntax appear, to a degree, as "mixed bags." One may still argue that, in the present context, the storage-related brain responses were elicited "only" by words rather than by longer stored constructions and the combinatorial ones by violations of rules of syntactic agreement between subject and verb, so that the two distinctions could be used interchangeably. However, in the wider context of brain language research, the storage/combination distinction captures those findings that seemingly contradict the lexicon/syntax opposition (Cappelle et al., 2010; Hanna & Pulvermüller, 2014; Leminen et al., 2013). Also, in the construction grammar framework, single words are seen as one type of construction on par with more syntactically complex ones, for example, argument structure constructions. The agreement construction "pronoun verb-affix" would be an elementary, but in this case, flexible member of this family (Goldberg, 2003; Goldberg, 2006). Although construction grammar subsumes storage-based and combinatorial mechanisms under the unifying key term of "constructions," there is room and need for distinguishing storage-related and combinatorial mechanisms. The present research result is consistent with a key idea immanent to most construction grammar frameworks, namely that "lexicon" and "grammar" are not modularly separated entities but dynamically interact from the earliest stages of linguistic understanding.

Conclusions

In a fully orthogonal MMN design, brain indices of early interactive effects of linguistic symbol retrieval and combination were manifest. Miniconstructions (i.e., minisentences), including stored words and not-stored pseudowords, as well as agreement between subject and verb or violation thereof, showed a modulation of the MMN response recorded while subjects tried to ignore acoustic target stimuli. These interactive effects of lexical and syntactic processing were present ca. 70–210 msec after onset of the critical syllable that first allowed subjects to detect the lexical/syntactic status of the strings. The present results are consistent with early interactive retrieval of whole linguistic symbols and processing of their combinations and sit comfortably with current theories in the construction grammar framework.

3. Study 2: Electrophysiological investigation of construction processing in the aphasic human brain

This chapter has been published as:

Lucchese G, Pulvermüller F, Stahl B, Dreyer FR, Mohr B. (2017). Therapy-induced neuroplasticity of language in chronic post stroke aphasia: a mismatch negativity study of (a)grammatical and meaningful/less mini-constructions. **Frontiers in Human Neuroscience**. 10:669. https://doi.org/10.3389/fnhum.2016.00669.

3.1 Introduction

Aphasia is an acquired language impairment that most commonly originates from stroke in the left hemisphere, affects approximately one third of all stroke patients, and leads to chronic disability (Berthier, 2005; Pedersen et al., 2004). As language and communication difficulties are particularly debilitating conditions, effective neurorehabilitation programs focusing on improving speech and language in patients with post stroke aphasia (PSA) are essential. According to recent reviews (Berthier & Pulvermüller, 2011; Brady, Kelly, Godwin, & Enderby, 2012), aphasia therapy is effective even when applied at the chronic stage and especially so if it is provided with high intensity, with > 5 therapy hours per week or even more (Bhogal, Teasell, & Speechley, 2003; Pulvermüller, Neininger, et al., 2001).

In several randomized controlled clinical trials, *intensive language action therapy* (ILAT; Difrancesco, Pulvermüller, & Mohr, 2012), also known as *constraint-induced aphasia therapy* (CIAT; Pulvermüller, Neininger, et al., 2001), has proven to be highly effective in ameliorating language deficits in chronic PSA (Berthier et al., 2009; Maher et al., 2006; Meinzer et al., 2007; Pulvermüller, Neininger, et al., 2001) as well as in subacute patients (Sickert et al., 2014). During ILAT/CIAT, aphasia patients practice verbal communication for ca. 15 hours per week by focusing on speech acts which are relevant for daily life activities, for example, making a request, or planning an action (Difrancesco et al., 2012). While the clinical benefit of ILAT/CIAT and the improvement of language functions has been robustly demonstrated and replicated (see above), additional evidence about the neuronal changes accompanying the documented functional restitution processes during ILAT/CIAT has recently been emerging, although many questions about the specific therapy-induced neuroplastic changes still remain unresolved. A better understanding of the neurobiological processes accompanying language deficits and rehabilitation may bear fruit in the development and advancement of neurorehabilitation programs (Berthier et al., 2009; Berthier & Pulvermüller, 2011; Cappa, 2011).

Unfortunately, neuroimaging studies on PSA indicate a fairly heterogeneous pattern of cortical reorganisation that seems to be modulated by patient characteristics, type of SLT, the language task applied, and the neuroimaging method (Crosson et al., 2005; Marcotte et al., 2012; Saur et al., 2006). Previous studies led to somewhat inconsistent results with regard to the contribution of the left (LH) and right (RH) hemispheres to language recovery (Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Saur et al., 2006; Weiller et al., 1995). Evidence for activation changes in fronto-temporal, perilesional regions of the LH during intense language therapy were reported in studies adopting different neuroimaging methods and paradigms (Breier et al., 2009; MacGregor et al., 2015; Meinzer et al., 2008; Mohr et al., 2016). Moreover, ILAT/CIAT–induced changes have been demonstrated in fronto-temporal areas of the RH not dominant for language with functional magnetic resonance imaging (fMRI) (Mohr, Difrancesco, Harrington, Evans, & Pulvermüller, 2014). Other studies reported ILAT/CIAT-associated brain activation changes in both hemispheres (Kurland, Pulvermüller, Silva, Burke, & Andrianopoulos, 2012; Pulvermüller, Hauk, Zohsel, Neininger, & Mohr, 2005). In one of these, single words presented in a lexical decision task elicited a negative going event-related potential (ERP) which increased over therapy, whereas brain responses to pseudowords remained unchanged, and the increase of both left- and right-hemispheric sources underlying the word-elicited ERP was positively correlated with the patients' clinical language improvements over treatment (Pulvermüller et al., 2005).

In summary, these studies have reported evidence for cortical reorganisation processes during intensive language therapy in both hemispheres, in a range of different linguistic tasks and across imaging methods. The involvement of perilesional perisylvian areas in the LH has strong support and is generally agreed upon, and there is also evidence for a contribution of the RH, not dominant for language (Berthier & Pulvermüller, 2011; Crinion & Leff, 2015). The more specific topographic location of functional restitution processes may indeed depend on the nature of the linguistic stimulus materials and tasks applied and/or the imaging technique used, but effects of these variables are still in need of explanation.

The reorganisation of language after stroke is best studied in patients with chronic aphasia, because in these patients it is unlikely that spontaneous restitution processes unrelated to neural plasticity (e.g., reduction of edema) influence the results. Note again that, in the chronic stage, i.e. > 1 year after aphasia onset, language improvements do normally not emerge spontaneously, although a range of studies demonstrated therapy-induced language improvements on clinical tests and concordant changes in neurophysiological indexes of language processing. Therefore, a particularly straightforward avenue for imaging the neuroplasticity of language is offered by intensive therapy regimes such as ILAT/CIAT, which are effective within a short period of time of a few weeks, so that any changes of health condition, mood, or social context are unlikely causes of any behavioral, linguistic, or neurophysiological change. Therefore, measuring language functions before and after intensive language therapy in chronic patients offers a unique avenue for studying the cortical reorganisation of language.

When investigating language in individuals with language impairments using an explicit task, there is some risk that the attempt of patients to solve the tasks, which they struggle with, leads to compensatory processes unrelated to language. Some of the RH activation dynamics previously observed across therapy have been attributed to such compensatory non-linguistic cognitive processes (see Crinion & Leff, 2015). Therefore, in order to avoid compensatory cognitive mechanisms that may confound the imaging of language functions, it is advantageous to use a task in which subjects passively process language and are therefore not encouraged to 'try hard' in their most challenging cognitive domain. In some previous studies, the MMN paradigm has been successfully applied to investigate automatic – or at least unattended – language processes (Pulvermüller, Kujala, et al., 2001; Shtyrov & Pulvermüller, 2002) in healthy individuals and in clinical groups. The MMN is the response to rare (deviant) acoustic stimuli in the context of frequent (standard) stimuli recorded in a passive listening task (Näätänen, 2001; Näätänen & Alho, 1995; Näätänen, Paavilainen, Rinne, & Alho, 2007) and is ideally suited for application in stroke patients who frequently suffer from attentional impairments (Näätänen et al., 2012; Näätänen et al., 2014). Linguistic MMN paradigms present spoken words or sentences passively while subjects are encouraged to attend elsewhere and can be used before and after intensive SLT to investigate language reorganisation in chronic patients over therapy. However, it has only been used in a few previous studies to map therapy-induced cortical changes in aphasia (MacGregor et al., 2015; Mohr et al., 2016). These previous studies found that, in PSA patients, the MMN to single spoken words increases over therapy and this increase reflects what is found in healthy subjects, where the MMN elicited by meaningful words is enlarged compared with physically matched but meaningless pseudowords (Endrass et al., 2004; Pettigrew et al., 2004; Pulvermüller, Kujala, et al., 2001; Pulvermüller et al., 2004; Shtyrov, Hauk, & Pulvermüller, 2004; Shtyrov, Pihko, & Pulvermüller, 2005; Shtyrov & Pulvermüller, 2002; Sittiprapaporn et al., 2003). These results suggest that lexical access and word form retrieval from verbal memory, a major linguistic function, are improved by SLT.

One may, however, argue that a true hallmark of language is not (only) the access to a vocabulary of spoken words; it is (in particular) the combinatorial capacity of individuals to build syntactically well-formed constructions from smaller meaningful units. It may be this latter capacity, which is particularly difficult to improve in language therapy efforts, that remains deficient in spite of successful vocabulary re-learning (see, for example, Dobel et al., 2001). One way to investigate combinatorial processing within the MMN paradigm is to compare syntactically well-formed grammatical strings with ill-formed, ungrammatical combinations (e.g., 'we come' vs 'we comes'). In healthy subjects, the MMN to grammatical strings is typically smaller compared with ill-formed combinations (Hanna, Mejias, et al., 2014b; Hasting et al., 2007; Menning et al., 2005; Pulvermüller & Assadollahi, 2007; Pulvermüller & Shtyrov, 2003; Pulvermüller et al., 2008; Shtyrov et al., 2003). In the present work, mini-phrases including a pronoun and a verb were used and lexical, along with syntactic, properties of these strings were varied. These mini-phrases were therefore meaningful and grammatically correct, or potentially meaningful but ungrammatical, or partly meaningless 'jabberwocky'-like sentences ending in a pseudoword (Marslen-Wilson, 1985). The hypothesis was that previous observations of therapy-related increases of word-induced MMN responses can be replicated when words are embedded into well-formed meaningful mini-constructions (e.g., *I walk*). In addition, the study presented here looked at the MMN to mini-constructions including a meaningless pseudoword, which, similar to jabberwocky sentences, are in part meaningless (*I nalk*). Critically, if grammatically legal but partly meaningless constructions show similar neuroplastic changes as fully legal strings, there would be evidence for reorganisation processes at the level of combinatorial or construction representations, over and above those previously reported for single words. Note, in this context, that jabberwocky strings induce both combinatorial/construction related processes and entail a degree of semantic understanding in spite of their meaningless elements (see Johnson & Goldberg, 2013, and Discussion below). For syntactically deviant strings however, no neuroplastic change over therapy was expected, given that combinatorial mechanisms appear to be linked relatively firmly to the left dominant hemisphere (Dobel et al., 2001; Pulvermüller, 1995; Tyler et al., 2011). Note that not all of the four linguistic conditions were predicted to reflect language reorganisation processes. In this case, any condition not revealing any therapy-related change could be used as baseline, against which the neurophysiological changes are interpretable.

3.2 Materials and Methods

Participants

Fourteen patients (6 females; mean age: 52 years), with chronic PSA (time post stroke > 1year) participated in the study. The datasets of four patients were either incomplete or so much contaminated by artifacts (trial rejection rate >20%) that they could not enter the analysis, thus leaving data from 10 patients for final analysis (see Table 3.1). Aphasia was diagnosed by a neurologist and was confirmed by the patients' profiles on the Aachen Aphasia Test (AAT; Huber, Poeck, & Willmes, 1983), a standard aphasia battery in German. All patients had suffered from a single stroke affecting the territory of the left middle cerebral artery and resulting in aphasia with different degrees of symptom severity. They were native speakers of German; one was bilingual. All patients were right-handed, as evaluated with the Edinburgh Handedness Inventory (Oldfield, 1971). Socio-demographic, clinical and lesion data are provided in Table 3.1. Lesion sites were determined by structural magnetic resonance imaging (MRI) scans. Lesions were of medium to large size (mean: 128.9 cm^3; SD: 103.23 cm^3) and involved the left-perisylvian language cortex including the frontal, temporal, insular and parietal cortices and underlying subcortical structures (internal capsule, deep white matter). Lesion overlay maps are presented in Figure 3.1. None of the patients had a lesion in the right hemisphere. Patients completed a four-week treatment protocol; clinical language tests were applied within 2-3 days before and after the therapy. Inclusion criteria were assessed at a pre-screening appointment where detailed study information was provided. All patients gave their informed consent. The study was approved by the Ethics Committee of Charité University Medical School, Berlin, and was conducted in accordance with the Declaration of Helsinki.

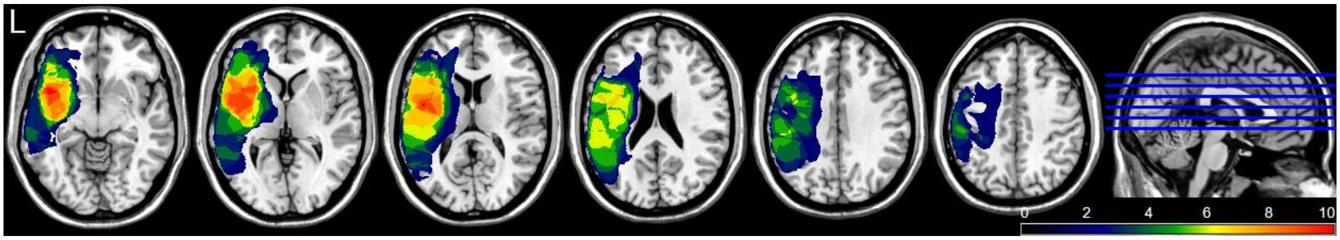

Figure 3.1. Lesion overlay maps of patients in different brain layers. Different colors indicate the number of lesion overlaps; red colored areas indicate lesion overlap regions in all 10 patients.

Pt.	Gender	Age	Education (years)	LQ	Diagnosis	Months after CVA	Lesion site	AAT		TT		Compr.		Naming		Repetition	
								Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	F	41	18	60	mild Broca's aphasia	97	LIFG, left IPC, and left STG	58.3	63.5	51	58	70	66	53	64	59	66
2	M	49	13	100	mild Broca's aphasia	52	LIFG and left STG	57.3	61.8	51	54	64	69	53	62	61	62
3	M	54	21	100	mild-moderate Broca's aphasia	49	Left MCA territory, TP	52.8	56.5	48	53	62	64	56	58	45	51
4	M	32	14	80	mild Broca's aphasia	40	LIFG and left IPC, insula	61.3	64.8	56	58	78	78	57	66	54	57
5	M	73	19	100	severe global aphasia	61	Left MCA territory, insula	39.5	42	41	41	34	41	41	40	42	46
6	M	51	12	100	moderate Broca's aphasia	42	LIFG and left STG and MFG, insula	48.5	58.3	51	54	49	60	49	69	45	50
7	M	63	13	100	moderate Broca's aphasia	31	LIFG and left STG, insula	50.8	57.8	54	53	48	57	49	59	52	62
8	F	47	12	80	mild Broca's aphasia	245	Left MCA territory, STG, MTG	61.0	64.0	55	59	62	65	68	71	59	61
9	F	37	11	100	mild-moderate Broca's aphasia	30	LIFG and left STG	54.3	58.8	54	58	57	57	53	61	53	59
10	M	65	25	80	moderate Broca's aphasia	239	Left MCA territory	48.5	51.0	47	48	49	51	46	49	52	56
	Mean ±SD	51.2 ±13	15.8 ±4.7	90 ±14.1		88.6 ±83		53.2 ±6.7	57.8 ±6.9	50.8 ±4.5	53.6 ±5.6	57.3 ±12.7	61 ±10	52.5 ±7.2	60 ±9.3	52.2 ±6.5	60 ±9.3

Pt. = Patient; LQ = Laterality Quotient; AAT= Aachen Aphasia Test; TT= Token Test; Compr. = Comprehension; CVA= cerebrovascular accident; LIFG = left inferior frontal gyrus; STG = superior temporal gyrus; IPC = inferior parietal cortex; TP = temporal pole; MCA = middle cerebral artery; SD = standard deviation

Table 3.1. Clinical and demographic data with overall and subtests' T-scores of the AAT (Huber et al., 1983) before and after therapy for each individual patient. (Token Test T-scores indicate: severe, 0–43; moderate, 44–53; light, 54–62; or mild ≥ 63 language disorder).

Therapy settings and clinical testing

Intensive language therapy was provided for four weeks, with 3.5 hours 3 days per week, thus 10.5 hours per week. Each patient participated in two different therapy methods focusing, respectively, on language-centered naming and communication-centered requesting. Request training consisted of action-embedded verbal communication relevant for daily activities adopting the ILAT/CIAT method (see Difrancesco et al., 2012). Language functions were assessed with the AAT by a clinician who was not involved in the therapy. Clinical testing and EEG recording took place within two days before and after the treatment interval. The AAT results before and after therapy are shown in Table 3.1. Clinical language changes over time were measured with four subtests of the AAT: Token Test (TT), Comprehension, Naming, and Repetition.

EEG Stimuli and Design

The critical 'deviant' stimuli in the MMN design were four short spoken German sentences including a pronoun and a verb. One stimulus was grammatically correct and contained a first person singular pronoun, followed by a correctly inflected verb (*SING*; *ich leide* = I suffer). A second sentence was also grammatically correct and contained a first person plural pronoun, followed by a correctly inflected verb (*PLUR*; *wir leiden* = we suffer). A third sentence contained a first person singular pronoun, followed by a verb-like meaningless pseudoword, an 'alexical' item not included in the German lexicon, that was correctly inflected and in agreement with the preceding pronoun (*ALEX*; *ich leige*). The fourth sentence consisted of a first person plural pronoun, followed by a real verb violating the inflectional agreement with the preceding pronoun and was therefore grammatically incorrect (*AGRA* ; *wir leide*). The lexical and grammatical status of the 4 critical sentences was disambiguated only after the onset of the final syllable that was used as the time-locking point for the ERPs. In order to avoid co-articulation effects that could provide cues about the word final syllable already during the word-initial one, the three words and the pseudoword were produced through cross-splicing and combination of syllables spoken in isolation. Multiple repetitions of the two pronouns (*ich* and *wir*) and of the four syllables *lei*, *de*, *ge*, and *den*, each spoken in isolation by a female native German speaker, were produced and a single token of each item was selected. Stimuli were recorded in an acoustically shielded chamber through a SM58 microphone (Shure, Niles, IL, USA). Adobe Audition CS5.5 (Adobe Systems Inc., San Jose, CA, USA) was used for stimulus editing. The recordings of the two pronouns (*ich* and *wir*) were each 210 ms long, with a fundamental frequency (F0) of 258 Hz each and an overall sound pressure of 17 dB. The inflection syllables “g*e*" and “*de*” were each 205 ms long, with a fundamental frequency F0 of 215 Hz and an overall sound pressure of 15 dB. The inflection syllable “*den*” lasted for 320 ms, with a F0 of 215 Hz and an overall sound pressure of 15 dB. The sound waveforms of the stimuli are presented in Figure 3.2

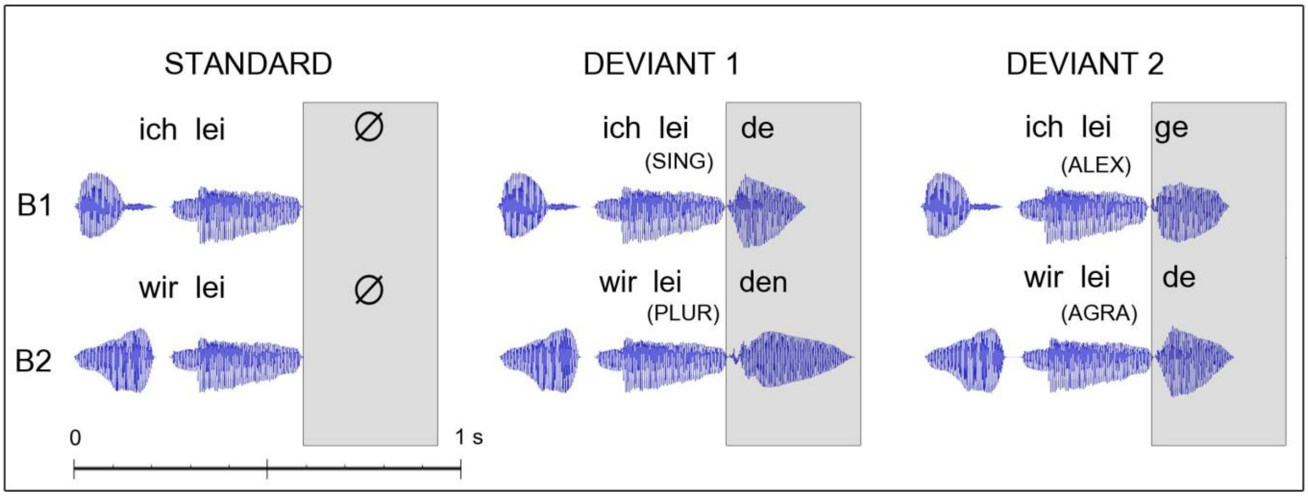

Figure 3.2. Acoustic waveforms for the standard and deviant stimuli as presented in the two blocks (B1 / B2 – constructions in first person singular / plural). The disambiguating point when information on lexicality of the critical last morpheme of the constructions became first available was at the onset of the last syllables of the constructions (as indicated in the box). ERPs were time locked to this last-syllable-onset point, which also corresponded to the point when deviant and standard stimuli first diverged. The following abbreviations are used: first person singular pronoun with correctly inflected verb (SING); first person plural pronoun with correctly inflected verb (PLUR); first person singular pronoun with correctly inflected pseudoword (ALEX) and a first person plural pronoun with incorrectly inflected verb (AGRA).

EEG recording

At each recording session, the four stimulus sentences were presented as deviant stimuli in an oddball MMN design in two blocks. In each block, a two syllable combination lacking the last disambiguating syllable provided the frequent standard stimulus, the background stimulus against which two different rare deviant stimuli were presented in random order. Therefore, one block included '*ich lei*' as standard and the SING and ALEX stimuli as deviants (*ich leide*; *ich leige*) and the other presented PLUR and AGRA (*wir leiden*; *wir leide*) against '*wir lei'.* The SOA of any two consecutive stimuli was 1095ms and the interval between the onset of any final syllable (the silent period after the "lei" in the standard stimuli) and the onset of the subsequent mini-string lasted 500 ms. In each block, each deviant (i.e. each of the 4 sentences) was presented 102 times with a probability of 12.5% amongst 612 repetitions of the standard. The order of standard and deviant stimuli was pseudo-randomized, with the constraint of a minimum of 2 and a maximum of 4 repetitions of the standard in between each two occurrences of the deviants. Each block started with 10 additional repetitions of the standard stimulus and had an overall length of ca 15 min. The two blocks were presented in a counterbalanced order across patients, keeping constant this order for each patient before and after the therapy.

The EEG was recorded (0.1-250 Hz band pass, 1000 Hz sampling rate) during acoustic stimulus presentation, in a dimly lit, electrically and acoustically shielded chamber through a 128-channel EEG setup (BrainProducts, Gilching, Germany) using 127 active electrodes mounted in an extended 10-05 system specific cap (ActiCap, BrainProducts, Gilching, Germany) and a reference electrode on the tip of the nose. One electrode was mounted at the level of the left infraorbital margin to record the electrooculogram (EOG). Impedances were kept below 5 kΩ. Patients were instructed to ignore the incoming acoustic stimuli and to focus their attention on a silent movie during EEG measurements. The pre- and post EEG recordings took place the day before the beginning of the therapy and immediately after termination of the therapy. The stimuli were presented using E-Prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA) through headphones at the sound level that each patient reported as comfortable and at which each patient reported to clearly detect the stimuli as probed with a few instances of a practice stimulus of the first block of the session.

EEG data processing

The EEG data were down-sampled offline to 200 Hz. Channels containing no signal or substantial artifacts (3 per recording on average) were rejected after visual inspection. The signals from the EOG electrodes were converted off-line to a bipolar vertical EOG signal by re-referencing it against the Fp1 electrode. The horizontal EOG was obtained by re-referencing the F9 against F10 electrode. An offline lowpass filter (25 Hz threshold, 4 Hz transition band) was applied. Epochs were time-locked to critical, final syllable onset, or silence onset after the first syllable in case of the standard stimuli, starting 100 ms before and ending 500 ms after the standard stimulus. The interval from -100 ms to 0 was used as baseline. Subsequently, independent component analysis (ICA) was performed resulting in 35 components and components correlating with the EOG signal (r>=0.3 or r<= -0.3) were rejected. (Hanna, Mejias, et al., 2014b; Hanna & Pulvermüller, 2014; Jung et al., 2000; Winkler, Haufe, & Tangermann, 2011). The dimensionality reduction was chosen to avoid over-fitting and to increase the reliability of the decomposition (Groppe et al., 2009; Onton, Westerfield, Townsend, & Makeig, 2006; Radüntz, Scouten, Hochmuth, & Meffert, 2015; Winkler et al., 2011) and the model order of 35 was chosen on the basis of previous similar applications (Hanna, Mejias, et al., 2014a; Winkler et al., 2011). EEG channels with artefacts that had previously been rejected were then spherically interpolated. Data processing as described above was carried out in Matlab R2012b (MathWorks, Natick, MA, USA) programming environment with EEGLAB 11.5.4.b (Delorme & Makeig, 2004). The following steps were carried out with the SPM8 suite (Litvak, Mattout, Kiebel, Phillips, Henson, Kilner, Barnes, Oostenveld, Daunizeau, & Flandin, 2011). Epochs with voltage variation of ±100 μV from 0 were rejected, leading to an average trial rejection rate of ca. 9% (ranging between 7-10% across sentence types and sessions). MMNs were calculated by subtracting the ERPs to the standard from the deviants in each block. The initial 10 standard repetitions in each block and the instances of the standard stimuli occurring immediately after a deviant were excluded from the averages. In order to assess the quality of ERP data, the signal to noise ratio, or SNR, was calculated for each patient as the ratio between the power of the signal and the noise estimated by averaging all trials after polarity reversal of every other trial (Schimmel, 1967; Viola, Thorne, Bleeck, Eyles, & Debener, 2011) at 150ms and from the electrodes chosen for analysis (see below for more details). This method of calculating the SNR is even more conservative than traditional SNR calculation from ERPs and has already found application specifically for estimating data quality in MMN linguistic research (Hanna & Pulvermüller, 2014). The average SNR across all patients was 13, thus indicating good data quality (Hanna & Pulvermüller, 2014).

Statistical analysis

Clinical language tests

As primary outcome measure, the results of the AAT before and after the treatment interval were compared using a *t*-test for dependent samples. A secondary analysis looked at the four subtests of the AAT separately using the same statistical procedure. The Bonferroni-Holm procedure was adopted for correcting for multiple comparisons (Holm, 1979) and adjusted values are reported throughout (Aickin & Gensler, 1996).

ERP/MMN analysis

The auditory and speech-evoked MMN has a typical fronto-central topography both in healthy individuals and in aphasic patients (Becker & Reinvang, 2007; Hanna, Mejias, et al., 2014b; Hanna & Pulvermüller, 2014; Näätänen, 1990; Pulvermüller & Shtyrov, 2006). Therefore, to target the expected maximum amplitudes of the MMN component and to examine laterality effects, 11 fronto-central electrodes (FFC1h, FFC3h, FCC1h, FCC3h, FCC5h, FC1, FC3, C1, C3, CCP1h, CCP3h) located directly on the left of the midline and the corresponding 11 homotopic electrodes over the right hemisphere were chosen for analysis. In line with previous studies (see above), the data showed the largest MMN amplitudes for these selected fronto-temporal electrodes. MMN amplitudes to the four sentences were analyzed in the 100-150 ms time window (MacGregor et al., 2015) by applying a repeated measures ANOVA with the factors *Laterality* (left versus right hemisphere) x *Sentence Type* (four string types: SING, PLUR, ALEX, AGRA) x *Therapy Session* (pre versus post therapy). Bonferroni-corrections were applied for post-hoc comparisons. Statistical analyses were performed with Statistica 12 software (Statsoft, Tulsa, OK, USA).

3.3 Results

Clinical language tests

After therapy, patients showed significantly improved language functions as assessed by the AAT mean scores [$t(9) = 5.14$; $p < 0.001$]. Analysis of subtest results confirmed this finding for all four subtests of the AAT, including the Token Test (TT); [$t(9) = 3.26$; $p = 0.01$], Auditory Comprehension [$t(9) = 2.43$; $p = 0.038$], Naming [$t(9) = 3.21$; $p = 0.01$], and Repetition [$t(9) = 4.76$; $p = 0.001$]. Pre-post therapy data of all subtests are displayed in Figure 3.3. In an additional analysis the robustness of the language improvement, behavioral data of those patients who were excluded from EEG analysis were included. The results of this analysis did not change the overall pattern of behavioural data (AAT, [$t(13) = 4.41$; $p < 0.001$]; TT, [$t(13) = 3.88$; $p < 0.001$], Comprehension, [$t(13) = 1.86$; $p = 0.042$]; Naming, [$t(13) = 3.11$; $p = 0.004$]; Repetition , [$t(13) = 3.98$; $p < 0.001$]).

ERP/MMN analysis

ERP curves and topographical maps of standard, deviant, and MMN responses for all experimental conditions are presented in Figure 3.4. MMN amplitudes were analyzed by a three-way repeated measures ANOVA which showed a significant *Laterality x Sentence Type x Therapy Session* interaction [$F(3,27) = 3.12$, $p=0.042$, $\eta p^2= 0.26$] (see Figure 3.5). The Mauchly's test indicated no violation of sphericity and therefore no correction for sphericity violation was needed. Post-hoc comparisons indicated that both grammatically correct sentences composed of a lexical item (*SING* and *PLUR*) elicited a significantly larger MMN response after therapy over the left hemisphere compared with before (*SING* LH: pre-post, p=0.046; *PLUR* LH: pre-post, p< 0.001). The *PLUR* condition also elicited an increased MMN response after therapy over the right hemisphere (RH: pre-post, p<0.001). Likewise, MMN activation to the well-formed but meaningless ‘jabberwocky’ string containing a pseudoword with correct inflection (*ALEX*) showed an increase over both hemispheres (LH: p<0.001, RH: p=0.002) over therapy. The MMN to the ungrammatical string (*AGRA*) did not show any significant changes in the pre- vs post- therapy comparison.

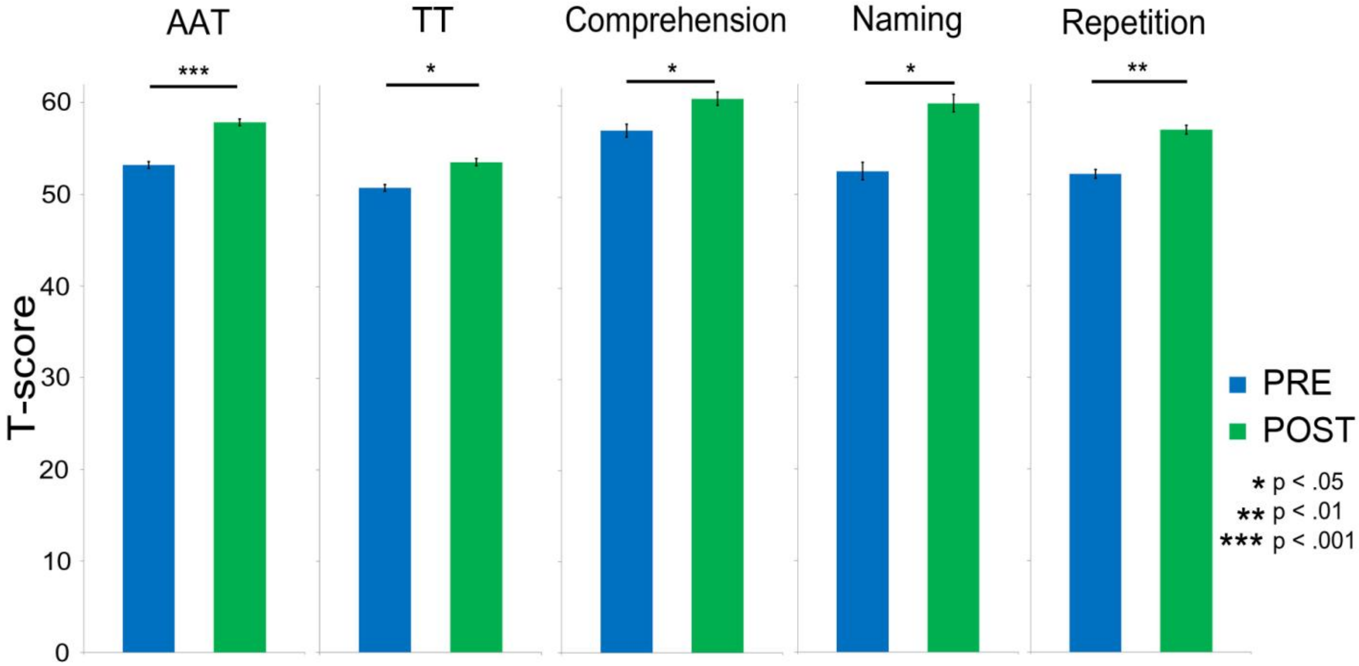

Figure 3.3. Bar charts showing the significant improvements in language abilities after treatment as assessed by the Aachen Aphasia Test (AAT) overall mean score and by all its four sections: Token Test (TT), Comprehension, Naming, and Repetition. Asterisks indicate statistical significance levels after Bonferroni-Holm's procedure (* p<. 05; ** p<. 01; *** p<. 001). Error bars show standard errors.

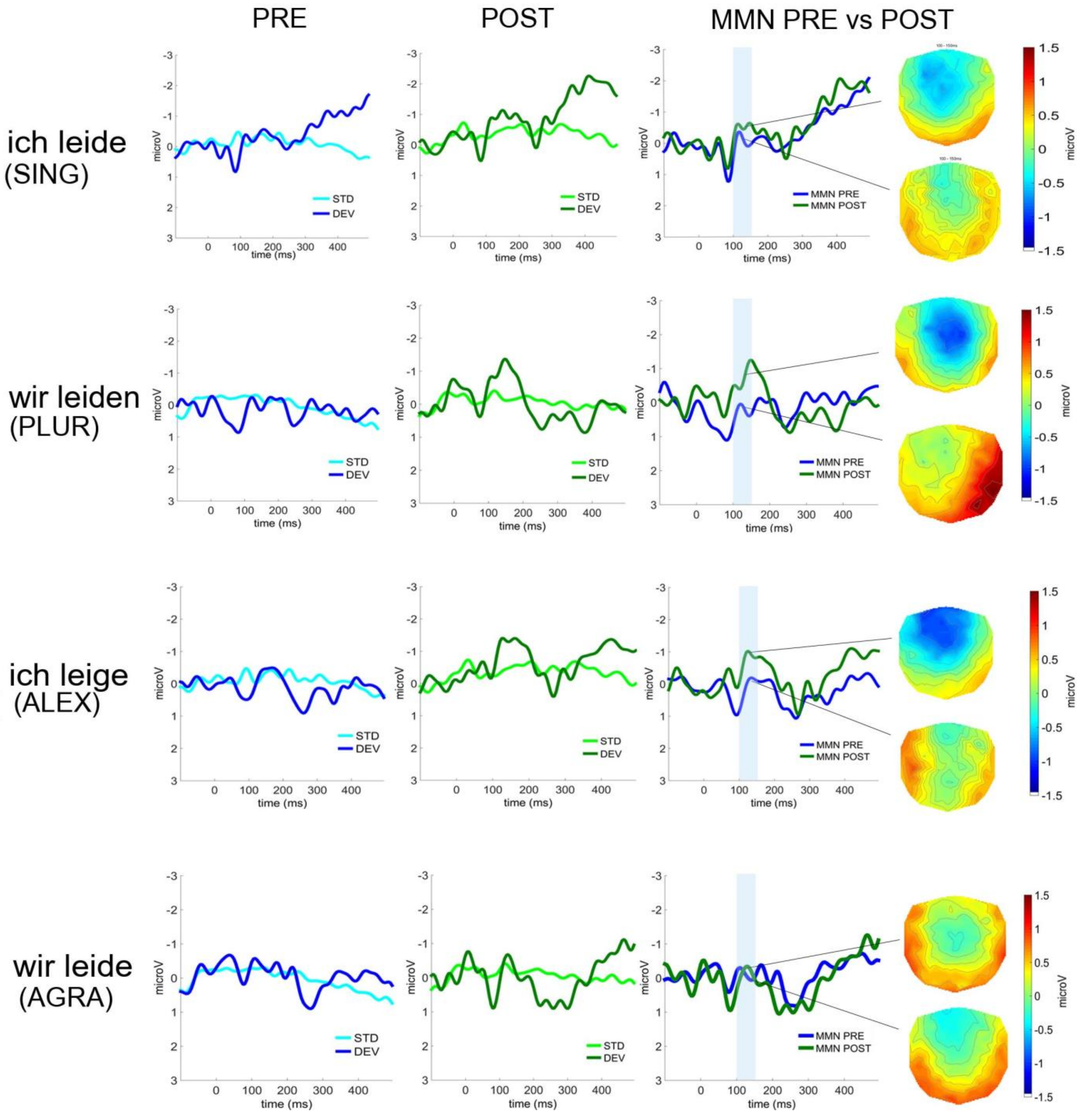

Figure 3.4. ERPs (average over 22 fronto-central electrodes) to deviant and standard stimuli before (left, in blue) and after therapy (middle, in green) for the four deviant sentence types (from top to bottom: SING; PLUR; ALEX; AGRA). The MMNs before (in blue) and after (in green) therapy and their scalp distributions are shown on the right. Time window chosen for statistical analysis are highlighted in light blue.

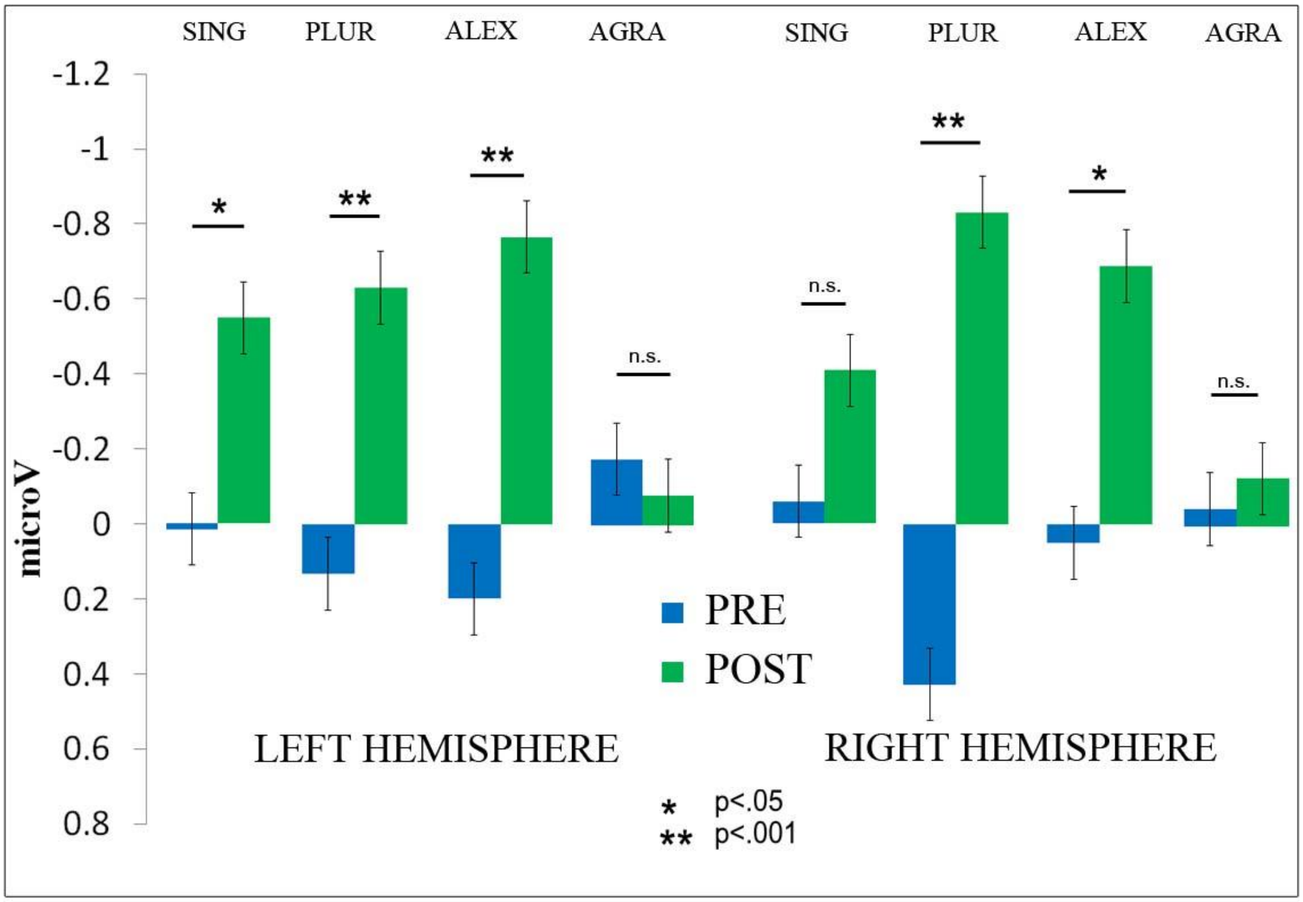

Figure 3.5. The significant interaction of Therapy session (post vs pre) x Laterality x Sentence type is displayed. The amplitude of the MMN increased on the left hemisphere for the SING condition, albeit with marginal significance, and on both hemispheres for the PLUR and ALEX conditions. No increase was found for the AGRA sentence type. Error bars show standard errors.

Correlations between clinical tests and MMN data

Spearman rank correlations were carried out between the clinical data (AAT overall scores and scores of the TT, Repetition, Naming, and Comprehension subsets) and the MMN amplitudes for each of the four sentence types in the 100-150 ms time window. Correlations were performed on the pre-therapy and post-therapy data and the post-therapy minus pre-therapy differences (for the right and left hemisphere). After correction for multiple comparisons, no correlations were significant.

3.4 Discussion

Using a passive non-attend oddball paradigm, this study found brain correlates of clinical language improvements in chronic post stroke aphasia patients, induced by intensive speech-language therapy. The MMN to grammatically well-formed and meaningful mini-constructions significantly increased over a 4 week therapy interval and a comparable increase was found for combinatorially regular 'jabberwocky' mini-constructions composed of a pronoun and an inflected but meaningless 'pseudo-verb'. In contrast, no neurophysiological changes across the therapy interval were evident from MMN responses to ungrammatical strings composed of meaningful words, which, however, violated syntactic agreement rules. Therefore, these results suggest that therapy-induced language reorganisation is restricted to meaningful and potentially meaningful constructions, but is blocked for strings that violate basic principles of grammatical combination.

Improvements on clinical language tests

In line with previous studies, the present results show that language abilities in chronic aphasia patients significantly improve after intensive language training administered over a relatively short period of time (Berthier et al., 2009; Breier et al., 2009; Kurland et al., 2012; Meinzer et al., 2008; Pulvermüller, Neininger, et al., 2001; Richter, Miltner, & Straube, 2008). Although the study did not include a control group without treatment, the conclusion on therapy-relatedness of the improvements seems relatively safe. First, the patient sample of the present study was, on average, 7.4 years post stroke (range 30 – 245 months) and it is well-known that spontaneous functional restitution is expectable up to ca. 1 year post stroke but is very rare later. Second, the outcome measure, the AAT, has very good retest reliability (Huber et al., 1983) so that a repetition effect on test performance can be excluded. The patients' improvement of clinical test scores therefore indicates that intensive SLT has a beneficial effect on language production and comprehension ability as measured with clinical tests of language function. When comparing the present results with previous work, it is important to highlight that, in the present study, a therapy frequency of ca. 10.5 hours per week was chosen but a relatively long therapy interval of 4 weeks was offered, whereas previous studies of intensive therapy, in particular ILAT / CIAT, typically used 2 weeks of 15 hours per week (Pulvermüller et al., 2001), however showing similar performance increase as in the present data set. These results indicate that a slight reduction in intensity together with an extension of the therapy interval do not necessarily lead to a change in benefits. However, this tentative suggestion needs precise testing in future work. As a further point to note, great care was taken in excluding from all therapy sessions the test items from the standard clinical test. Therefore, and in contrast to some previous studies reporting 'trivial' therapy/training effects on test items also used during therapy, the present clinical test performance shows generalization of therapy effects to not-practiced items.

MMNs to mini-constructions signal language restitution

Improvements on language tests were accompanied by electrophysiological changes as measured by the MMN. A significant increase of MMN amplitudes to grammatically correct sentences was observed over both hemispheres, with more pronounced changes being manifest in the recording on the left than on the right. No therapy-related MMN changes were obtained for syntactically incorrect, ungrammatical strings. While consistent with earlier findings of increased ERP responses to words after intensive language action therapy (MacGregor et al., 2015; Mohr et al., 2016; Pulvermüller, Hauk, et al., 2005), the present data go beyond the single word level and extend previous research to the level of sentence processing, also offering information about the neurodynamics of the processing of inappropriate grammatical and semantic context. As language-related neurophysiological changes over therapy were observed within approximately 200 ms after critical words and whole constructions could first be recognized from the acoustic input, the present results are consistent with an increasing body of evidence on spoken language processing, which shows that lexico-semantic and combinatorial syntactic properties of sentences affect neurophysiological brain activity early-on and in an interactive fashion (Guajardo & Wicha, 2014; Hagoort, 2003; Palolahti et al., 2005; Wicha, Moreno, & Kutas, 2004)

As mentioned, the chronic stage at which all of the patients partaking in the present study were tested and trained (> 1 year post stroke; mean duration of illness: 7.4 years), discourages interpretations in terms of spontaneous remission processes. This does apply not only, as argued above, to clinical test results but, in the very same way, to the neurophysiological changes observed. Stability of clinical and neuronal activation patterns has been indeed repeatedly demonstrated in chronic aphasic patients outside of therapy periods (Breier et al., 2009; Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006; Meinzer, Djundja, Barthel, Elbert, & Rockstroh, 2005) and this is consistent with an interpretation of the present findings as attributable to specific therapy-induced neuroplasticity. Furthermore, it should be noted that four lexico-semantically and syntactically different experimental conditions were employed in the MMN paradigm, which served as control conditions within the experimental design. If MMN enhancements after therapy occurred due to unspecific effects, for example related to repetition or changes in task strategies or attention, similar alterations of neurophysiological responses across all four conditions would have been expected. However, this was not the case, as the asyntactic agreement violation condition failed to elicit any treatment-related MMN changes. Importantly, it is not possible to explain the increase of construction-elicited MMNs across therapy as a pure repetition effect. One may argue that memory traces may have formed for this pseudoword contained in this specific sentence (Kimppa, Kujala, Leminen, Vainio, & Shtyrov, 2015; Shtyrov, 2011), thus leading to enhanced MMN brain responses (Shtyrov, Nikulin, & Pulvermüller, 2010). However, similar to other non-specific explanations, this one would also predict MMN increases for ungrammatical constructions composed of real words, which the data presented here did not confirm.

Therefore, due to the inclusion of a within-subject control condition, which failed to lead to neuroplastic changes, an unspecific (e.g.,mere repetition or general learning) effect can be ruled out as explanation of this set of results. Therefore, the ERP enhancement over time and therapy documented here and in previous studies (Pulvermüller et al., 2005; MacGregor et al., 2015; Mohr et al., 2016) suggests an interpretation in terms of neuroplastic changes underlying the processing of the specific types of words and constructions tested. .

In a previously mentioned study, which recently reported lexical MMN indices of words and pseudowords processing across ILAT, MacGregor et al. (2015) found a therapy-induced left-lateralized MMN enhancement specifically to words (but not pseudowords) after therapy. This word-related MMN enhancement is consistent with the present results on legal constructions, as the significant Laterality x Sentence type x Therapy session interaction demonstrated enhancement of MMN amplitudes after therapy for those well-formed sentences made up of legal lexical items exclusively. Also the previously seen leftward laterality pattern (MacGregor et al., 2015), was in line with the present one, as the MMN enhancement in the present study was stronger over the LH compared to the RH. However, somewhat in contrast with previous data (MacGregor et al., 2015; Pulvermüller et al., 2005), the present study also revealed a post-therapy increase of the MMN activation in response to the sentence containing a pronoun followed by a correctly inflected pseudoword. Note again that, in MacGregor's work, no therapy-induced changes were seen for single stand-alone pseudowords. Why, then, should pseudowords in construction context elicit brain indexes of neuroplastic changes similar to those of meaningful words and constructions?

Obviously, the critical difference between studies and conditions is the presence/absence of a context, in which pseudowords were embedded. In the present work, pseudowords were preceded by a pronoun, which was syntactically congruent with, and showed agreement with, the inflected 'pseudo-verb'. Hence, patients had the opportunity to integrate the perceived meaningless 'pseudo-verbs' into a construction context. That senseless 'jabberwocky' sentences containing no content words at all still induce a degree of semantic processing is obvious from the fact that they specifically prime meaningful verbs that fit into the same construction schema (Johnson & Goldberg, 2013). Accordingly, a construction including a meaningless pseudoword (such as *ich leige* – where ‘*leige*’ by itself is meaningless) would activate a construction schema (for one-place verbs), which, in turn, semantically primes meaningful verbs typically appearing in this type of construction (one-place verbs such as *liegen*, *schlafen*, *leiden* etc. (‘to rest, sleep, suffer …’). In this perspective, it would be the activation of an abstract construction schema, or argument structure construction, that leads to a trace of understanding of pseudoword-containing ‘jabberwocky’ constructions. The therapy-related restitution of the neuronal circuit underpinning the construction schema would be the underlying neuroplastic mechanism. Although this hypothesis is in need of further investigation, it offers a unique integration of both findings mentioned, the absence of MMN increases across therapy for stand-alone pseudowords, and its presence for construction embedded ones. Crucially, the conclusion offered by the newly observed jabberwocky-induced increase of the Mismatch Negativity is that grammatical processes at the level of constructions are subject to neuroplastic changes during therapy of chronic aphasia. In future studies, it will be of the essence to investigate the neurodynamics of pseudowords in and out of construction context during aphasia therapy in the same patients.

Note that strings with grammatical violation only included words and morphemes with legal lexical status. Out of context, these items would all have been expected to show enhancement of lexical MMN responses over therapy. Therefore, it appears that the combinatorial irregularity – the violation of morpho-syntactic agreement rules implemented in the ungrammatical (AGRA) string and/or the failure of accessing a construction schema – blocked the appearance of any signs of neuroplastic change.

One may argue that a classic linguistic ‘words and rules’ approach to language (Pinker, 1997) may offer an alternative explanation to the enhancement of ‘jabberwocky’-elicited MMNs across aphasia therapy. In this view, the neuroplastic dynamics could be attributed to the combinatorial rule linking together pronoun and verb affix. However, the established neurophysiological indexes of grammar processing are enhancements of brain responses – i.e., an enhanced MMN or, similarly, early N100 or left anterior negativity (ELAN) – to *un*grammatical strings as compared with legal ones (Friederici, 2011; Hasting & Kotz, 2008;

Neville et al., 1991; Shtyrov et al., 2003)[5]. Therefore, based on the pre-existing literature, if neuroplastic changes make rule processing mechanisms more efficient, the prediction is that a 'syntactic' MMN or ELAN to *un*grammatical strings increases in size across therapy. Evidently, the present data do not support this hypothesis, as MMNs to ungrammatical combinations were not significant before therapy and remained absent after, which contrasts with the therapy related enhancement of MMNs to jabberwocky constructions. This pattern of neurophysiological changes is difficult to attribute to a combinatorial rule processing mechanism. However the construction-centered perspective attributing the MMN increase to a consolidating abstract combinatorial-semantic construction schema sits well with the absence of MMN dynamics for ungrammatical strings, because an ungrammatical string may impact on the access of construction schemas and their associated semantics, and such access failure may be reflected in smaller MMNs (see Hanna, Shtyrov, Williams, & Pulvermüller, 2016; Pulvermüller & Shtyrov, 2006 for discussion). Note that, contrary to classical syntax, construction grammar scientists assume an intrinsic connection between the form and semantic function of sentences (Goldberg, 2006) so that any grammatical violation has implications for understanding.

Similar to one previous study (MacGregor et al., 2015), but in contrast to other previous research (Pulvermüller et al., 2005; Mohr et al., 2016), correlations between clinical outcome measures and ERP/MMN amplitudes did not yield any significant results. This might be attributable to either the lack of statistical power in the small patient group in the present study or the passive nature of the MMN paradigm as opposed to active engagement of the patient in clinical assessment (Breier, Maher, Schmadeke, Hasan, & Papanicolaou, 2007; MacGregor et al., 2015). Indeed, the significant positive correlation between language improvement and word-specific N250 enhancement during an active lexical decision task (Pulvermüller, Hauk, et al., 2005) points towards this interpretation of data. However, Mohr et al. (2016) found clinical neurophysiological correlations for word-elicited MMNs as recorded with MEG and clinical measures in a slightly larger patient sample. In future, it will be essential to attempt at

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[5] MMN and ELAN are related indicators of syntactic processing (Hasting & Kotz 2008), however, the MMN is elicited under distraction whereas ELAN is typically recorded in attention demanding tasks (Pulvermüller & Shtyrov, 2006).

further improving signal to noise ratios of the neurophysiological data obtained in patients, so that, ideally, any systematic relationship between the language performance of single subjects and their neurophysiological results could become easier to track. This is particularly important in view a possible future use of MMN and similar measures as biomarkers of language proficiency at the single subject level (Bishop, 2007). The present findings can only be seen as a very first step towards this aim. A further limitation of the present work relates to the standard clinical language tests applied, which do not systematically separate and specify lexical, syntactic and semantic processes and abilities. Using more detailed behavioural testing of specific psycholinguistic processes, it might be possible to detect correlations between any of these and the neurophysiological indexes of rather specific construction types.

Patients in the present study were, on average, slightly younger than in previous studies. However, based on previous data from older patients with aphasia who received intensive language therapy, it seems that patients benefit from treatment and show neuroplastic changes after therapy, irrespective of their age. (Breier et al., 2007; Marcotte et al., 2012; Sickert et al., 2014). Still, future research is necessary to clarify whether the present therapy-induced ERP changes to well-formed meaningful strings and partly meaningless strings conforming to a construction pattern can be replicated in a larger population and across age groups.

Conclusions

The present findings confirm that language therapy improves language functions in chronic PSA when administered at high intensity over a short period of time. Crucially, an increase of brain activation during automatic sentence processing emerged after treatment, indicating restitution of language functions. Clinical language improvements were reflected by enhancements of post-therapy lexical MMN amplitudes especially over the left and also, to a lesser degree, the right hemisphere. In particular, the MMNs to different sentence types allowed us to draw careful inferences on the neuroplasticity of different cognitive-linguistic functions, especially on the consolidation of neuronal circuits for lexical items and constructions. The present study suggests that the MMN has potential to become a neurophysiological biomarker of language recovery and cortical reorganisation in chronic post stroke aphasia, but equally shows the need for further research and studies at an individual patient level to further explore this potential.

4. Study 3: Electrophysiological investigation of construction processing in the modelled human brain

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4.1. Introduction

Experimental evidence suggests that the cortex stores knowledge about meaningful, well-known familiar items (such as objects, faces, and words) as distributed memory circuits, that is, strongly interlinked neuronal ensembles of hundreds or thousands of neurons whose members may be spread across distant areas of cortex. The reactivation of such a cell assembly (CA) circuit sparked by the perception of the corresponding sensory item is hypothesized to induce waves of reverberant activity within the corresponding circuit (Hebb, 1949), measurable as correlated firing activity. Intracortical recordings of stronger high-frequency synchronous oscillations during perception of coherent vs. incoherent visual stimuli were thus taken as crucial support for the existence of such mutually supporting neuronal ensembles in the brain (Buzsaki & Draguhn, 2004; Engel & Singer, 2001; Singer, 1993; Singer & Gray, 1995; Varela, Lachaux, Rodriguez, & Martinerie, 2001). In the cognitive domain, observed increases in the oscillatory cortical responses to meaningful, well-known stimuli compared to senseless, unknown sensory material also provide evidence for the existence of stimulus-specific memory traces for frequently occurring percepts (and lack thereof for novel, unfamiliar ones) (Bertrand et al., 2013; Craddock et al., 2015; Hassler et al., 2011; Henson et al., 2009; Krause et al., 1998; Pulvermüller et al., 1994; Tallon-Baudry, 2009). The majority of experiments testing this hypothesis focus on fast oscillatory activity, even though other types of correlation can also exist (Abeles, 1991). In particular, differences in spectral responses have typically been found in the so-called gamma band (around 40 Hz), but also in the low-gamma and high-beta (20-30Hz) and very high gamma (above 100 Hz) bands, across different modalities and using different recording methods. In the visual domain, the role of gamma-band activity has been intensively researched: a number of studies have reported differences in oscillatory responses to recognizable, coherent, complete, meaningful stimuli vs. unrecognizable, scrambled, incoherent or incomplete visual ones, including, e.g., real or illusory (Kanizsa) triangle and no-triangle (Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996), pictures and fragmented images (Bertrand et al., 2013; Gruber, Muller, & Keil, 2002), objects and non-objects (Craddock et al., 2015), and faces vs. scrambled faces (Gao et al., 2013; Henson et al., 2009). Notably, only responses to the coherent stimuli have been found to induce synchronous oscillations across neurons located in different cortical hemispheres (Supp et al., 2005; Supp, Schlögl, Trujillo-Barreto, Müller, & Gruber, 2007).

High-frequency dynamics like gamma oscillations have been implied in the recognition of familiar sensory items also in the language domain, with meaningful words consistently inducing stronger spectral responses than senseless, unknown pseudoword items for frequencies between 20 and 40 Hz (Eulitz et al., 1996; Krause et al., 1998; Lutzenberger, Pulvermüller, & Birbaumer, 1994; Pulvermüller, Eulitz, et al., 1996), and, occasionally, even in higher frequency ranges (up to 200 Hz: Canolty et al., 2007; Mainy et al., 2008). Some studies suggested that aspect of the meaning of words might be reflected in different high-frequency response topographies and long-range gamma synchrony across the cortex (Pulvermüller, Preissl, et al., 1996; Weiss & Mueller, 2013); the suggestion here was that the underlying neuronal circuits carrying words and their meaning might be differentially distributed across cortical areas depending on the semantic category of the stimulus.

This study focuses on the manifestation of the above-mentioned differences in oscillatory behaviour as observed in the linguistic domain. In particular, the main goal of the present study is to reproduce the neurophysiological findings of larger spectral power for words than pseudowords observed in the 20-40 Hz range using a neuroanatomically realistic computational model of the cortex, and examine the model's behaviour at the cortical-circuit level to shed some light on the underlying neural mechanisms. Recent simulation results obtained using biologically realistic models of the left-perisylvian ("language") cortex similar to the one used here have mechanistically demonstrated the spontaneous formation and activation dynamics of distributed memory circuits for words, which emerged in the network as a result of Hebbian learning (Hebb, 1949) and simulated "sensorimotor" experience (Garagnani & Pulvermüller, 2011, 2016; Garagnani et al., 2007, 2008; Tomasello, Garagnani, Wennekers, & Pulvermüller, 2016). The hypothesis was that, if the difference in high-frequency responses induced by familiar vs. unfamiliar items can be related to the presence of memory traces for the former and absence thereof for the latter, the same computational model should be able to reproduce the above-mentioned experimental findings, potentially providing an explanatory account for the enhanced high-frequency brain responses to lexical items on the basis of the activation of such stimulus-specific cell-assembly (CA) circuits.

Gamma oscillations and their synchronization have been investigated computationally and theoretically in numerous studies (Buzsaki & Wang, 2012 for reviews; see Wang, 2010). Oscillations easily occur in simulations of networks of spiking neurons, regardless of whether these are made up of simple leaky integrate-and-fire (LIF) cells or more complex neuron types (Herman, Lundqvist, & Lansner, 2013; Izhikevich & Edelman, 2008; Sommer & Wennekers, 2001; e.g., Traub et al., 2000). Various mechanisms for the origin of oscillations in the gamma range are known: Brunel (2000), for example, has mathematically analysed the quite generic case of two pools of excitatory and inhibitory LIF neurons. While the use of excitatory and inhibitory populations is very common in computational studies, including the present one, further mechanisms have been also proposed as potential sources of cortical gamma oscillations, such as synaptic inhibition and correlation-induced stochastic synchrony (Wang, 2010; Whittington, Cunningham, LeBeau, Racca, & Traub, 2011).

A variety of localist and distributed connectionist models have been proposed in the past to explain the putative mechanisms underlying speech processes (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Gaskell, Hare, & Marslen-Wilson, 1995; e.g., McClelland & Elman, 1986; Norris, 1994; Page, 2000; Plaut, McClelland, Seidenberg, & Patterson, 1996; Rogers et al., 2004; Seidenberg & McClelland, 1989; Seidenberg, Plaut, Petersen, McClelland, & McRae, 1994; see Woollams, 2015 for a recent review). One of the earliest, most influential connectionist models of memory (McClelland & Rumelhart, 1985), for example, was able to account for basic differences in repetition priming of spoken words and pseudowords (a word being represented as a distributed pattern of activity across a layer of units). Nowadays, a new generation of large-scale neural-network models are being increasingly used in the study of memory and language processes (e.g., Herman et al., 2013; Hinaut et al., 2015; Pulvermüller & Garagnani, 2014; Rolls & Deco, 2015; Wennekers, Garagnani, & Pulvermüller, 2006), which are able to elucidate the underlying brain mechanisms on the basis of neurobiologically realistic learning and anatomical connectivity, and explain neuroimaging data (Garagnani & Pulvermüller, 2016; Husain, Tagamets, Fromm, Braun, & Horwitz, 2004; Pulvermüller, Garagnani, & Wennekers, 2014). However, to date, a neuromechanistic account directly linking the different high-frequency neurophysiological responses induced by familiar word and unknown pseudoword stimuli to corresponding differential oscillatory behaviour of underlying large-scale neuronal populations is still missing.

4.2. Materials and Methods

General structure and features of the model

A neural network architecture was used to simulate cortical mechanisms underlying language function in the left hemisphere of the human brain (Figure 4.1A). The network is divided into twelve identical "areas" of spiking artificial neurons with reciprocal connections between and within them (see Figure 4.1A). Each area consists of two "banks" or layers of excitatory and inhibitory cells. The model was constructed so as to reflect a range of properties of the human cortex; the main features included: (1) local (see Figure 4.1D) and area-specific global inhibitory mechanisms (Braitenberg, 1978b; Yuille & Geiger, 2003); (2) patchy, random and topographic connections, with probability of a synaptic link being established between two cells decreasing with their distance (Braitenberg & Schüz, 1998; Kaas, 1997); (3) presence of uniform noise (simulating spontaneous, baseline neuronal firing) in all network areas at all times (Rolls & Deco, 2010); and (4) Hebbian synaptic plasticity, simulating well known phenomena of long-term potentiation (LTP) and depression (LTD) (Artola & Singer, 1993). These features are identical to those used in previous versions of the architecture (Garagnani & Pulvermüller, 2011, 2013, 2016; Garagnani et al., 2008). Excitatory neurons are now modelled as leaky integrate-and-fire cells with adaptation, whereas previous simulations used a "lumped" or mean-field approach, with each cell representing the average activity of a local pool or cluster of neurons (Eggert & van Hemmen, 2000; Wilson & Cowan, 1973). In line with the introduction of spiking cells, the present model also implements a revised version of Hebbian learning, in which the presence of a pre- or post-synaptic spike is a necessary (but not sufficient) pre-requisite for any synaptic changes to take place. The full formal specification of the model is provided in the Appendix at the end of this dissertation.

During speech production, patterns of neural activity co-occur in primary motor and auditory cortices as a consequence of the articulatory movements and simultaneous perception of the corresponding uttered sounds; hence, both of these primary perisylvian areas (labelled M1i and A1, respectively) were modelled. Furthermore, as the processing of information about the referential meaning of object-related words (such as “flower”) involves primary visual cortex, and because execution of the action corresponding to the meaning of words such as “run” or “grasp” is controlled by the more lateral and superior aspects of the motor cortex, the model also included primary visual (V1) and dorsolateral motor ($M1_L$) cortices (see Figure 4.1.A). In addition to these four primary areas, “higher” secondary and multimodal cortices which are known to have direct anatomical links with the above four primary sensorimotor cortices were also included (see below for details and supporting neuroanatomical evidence). These were secondary inferotemporo-occipital visual, auditory belt, and inferior and lateral premotor cortex (TO, AB, PM_i, PM_L) and respectively adjacent multimodal anterior-temporal, superior-temporal (auditory parabelt) and inferior and dorsolateral prefrontal cortices (AT, PB, PF_i, PF_L).

The present model builds upon and extends an existing architecture recently used to simulate neural mechanisms underlying acquisition of action- and visually-related words (Garagnani & Pulvermüller, 2016; Tomasello et al., 2016). The present study further augments the architecture by introducing (i) additional between-area connections, and (ii) spiking artificial neurons. This level of granularity was deemed appropriate to simulate the phenomena of interest here, namely, the spontaneous emergence of synchronous oscillations in cortically distributed neuronal populations.

As in all previous versions, care was taken to implement *only* mechanisms reflecting well-documented neurophysiological phenomena. Crucially, the network’s connectivity structure (depicted by black and purple bidirectional “arrows” in Figure 4.1B) closely reflects existing anatomical pathways between corresponding areas of the cortex, with between- and within-area synaptic projections mimicking known properties of the mammalian brain.

The previous mean-field versions of the architecture (Garagnani & Pulvermüller, 2016) only realised a subset (thick arrows in Figure 4.1.B) of the connections implemented here, that is, reciprocal links between next-neighbour areas within each triplet of the four "modality-specific" sub-systems modelled (thick black arrows in Figure 4.1B), and reciprocal links between anterior temporal (AT), superior parabelt (PB), and inferior (PF_i) and superior-lateral (PF_L) prefrontal areas (thick purple arrows in Figure 4.1B). The neuroanatomical evidence documenting presence of such links is reported in Appendix A. In addition to these, the following between-area anatomical connections are also modelled in the present version (thin arrows in Figure 4.1B):

- links between non-adjacent areas within the superior- or inferior temporal, superior or inferior frontal, cortices (i.e., within-modality "jumping" links), connecting primary auditory (A1) with parabelt (PB) areas (Pandya & Yeterian, 1985; Young, Scannell, Burns, & Blakemore, 1994), lateral/inferior prefrontal ($PF_{L/i}$) with corresponding primary motor areas ($M1_{L/i}$) (Deacon, 1992; Guye et al., 2003; Young, Scannell, & Burns, 1995), and primary visual (V1) with anterior temporal (AT) cortices (Catani, Jones, Donato, & Ffytche, 2003; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004);

- long-distance connections between "auditory" (superior temporal gyrus) and "articulatory" (inferior frontal gyrus) perisylvian regions – specifically, linking parabelt (PB) with inferior premotor (PM_i) areas (Glasser & Rilling, 2008; Petrides & Pandya, 2009; Saur et al., 2008; Saur et al., 2010) and belt (AB) with inferior prefrontal (PF_i) areas (Kaas & Hackett, 2000; Rauschecker & Scott, 2009; Romanski, Bates, & Goldman-Rakic, 1999);

- long-distance links between extrasylvian "visual" (inferior-temporal, TO, AT) and "motor" (dorsolateral prefrontal and premotor, PF_L/PM_L) cortices, analogous to those listed above for the perisylvian ("auditory" and "articulatory") systems, documented by both neuroanatomical (Makris & Pandya, 2009; Pandya & Barnes, 1987, p. p.49; Seltzer & Pandya, 1989) and inactivation studies in the macaque monkey (Bauer & Fuster, 1976, 1978; Chafee & Goldman-Rakic, 2000; Fuster, Bauer, & Jervey, 1985; Fuster & Jervey, 1981).

Results from previous simulation studies have shown that, when repeatedly confronted with activity patterns to their "primary" (input) areas, networks including the above range of neurobiologically realistic features exhibit spontaneous formation of distributed associative circuits (Garagnani & Pulvermüller, 2016; Garagnani et al., 2007, 2008; Garagnani, Wennekers, et al., 2009; Tomasello et al., 2016), or "cell assemblies" (CAs) (Hebb, 1949), networks of cells binding together patterns of frequently co-active neurons (Braitenberg, 1978a; Hebb, 1949; Palm, 1982). These circuits, which emerge as a result of correlational learning mechanisms, exhibit non-linear functional behaviour, with two quasi-stable states ("on" and "off") (Garagnani et al., 2007, 2008; Garagnani, Wennekers, et al., 2009; Pulvermüller & Garagnani, 2014).

The previous, mean-field versions of the architecture exhibited the spontaneous formation of such lexico-semantic circuits in the context of simulated acquisition of object- and action-related words (Garagnani & Pulvermüller, 2016; Tomasello et al., 2016). In particular, the resulting CAs showed category-specific distributions, linking up "auditory-articulatory" patterns (simulating neural activity induced in M1i by word production and correlated activity in A1 due to perception of the corresponding sound) with semantic information present either in the model's perceptual (V1, object words) or motor ($M1_L$, action words) areas. During simulated word-comprehension processes, reactivation of these circuits sparked the model's primary sensorimotor areas in a category-specific fashion, reflecting the patterns of activity that occurred in the network at word-learning stages (Garagnani & Pulvermüller, 2016; Tomasello et al., 2016).

Here, the network was trained following the same procedure used in the previous studies; as a result of the learning mechanisms, similarly distributed CAs emerged in this extended spiking architecture. After training, the network's oscillatory responses to learned, meaningful, "word" patterns and novel, meaningless "pseudoword" stimuli (see Section *Simulating Learning of Meaningful Words* below) were recorded and analysed, in the attempt to shed some light on the neuromechanistic causes underlying experimentally observed differences.

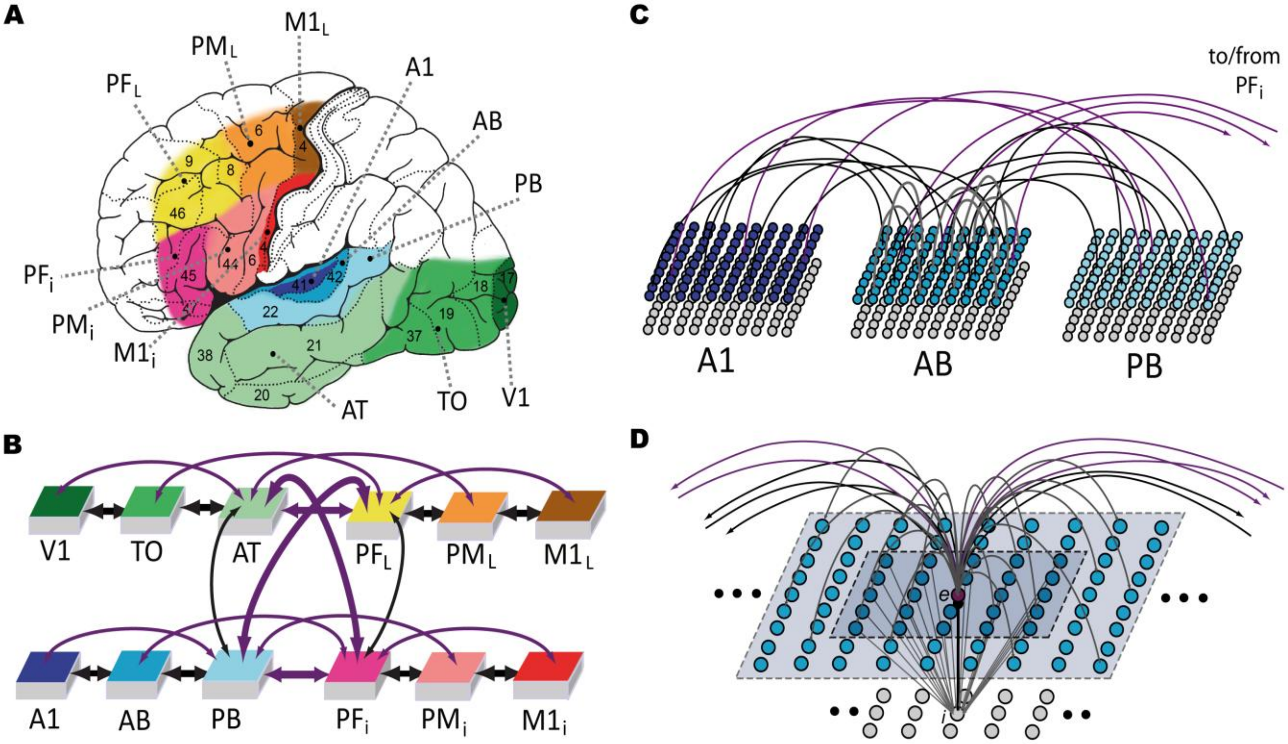

Figure 4.1. Model of lexical and semantic mechanisms: The 12 cortical areas simulated (A), their global connectivity architecture (B), aspects of between- (C) and within-area (D) connectivity of model neurons are illustrated. (A) Six *perisylvian* and six *extrasylvian* areas are shown, each including an anterior (frontal) and a posterior (temporal) part. Perisylvian areas include three areas in inferior frontal gyrus (coloured in different shades of red), including inferior-prefrontal (PF$_\mathrm{i}$), premotor (PM$_\mathrm{i}$) and primary motor cortex (M1i) and three areas in the superior temporal lobe (shades of blue), including auditory parabelt (PB), auditory belt (AB) and primary auditory cortex (A1). These areas are relevant for storing and linking up articulatory-phonological and corresponding acoustic-phonological patterns of neuronal activations, which co-occur, for example, when spoken word forms are being articulated (activity in M1i) and corresponding speech sounds are simultaneously perceived (stimulation of primary auditory cortex, A1). Extrasylvian areas include three areas in lateral/superior frontal cortex (yellow to brown), including dorsolateral prefrontal (PF$_\mathrm{L}$), premotor (PM$_\mathrm{L}$) and primary motor cortex (M1$_\mathrm{L}$) and three areas forming the occipito-temporal (“what”) visual stream of object processing (different shades of green), including anterior-temporal (AT), temporo-occipital (TO) and early visual areas (V1). These areas contain neural patterns carrying semantic information (word meaning), for example when words are used (activity in all perisylvian areas) to talk about objects present in the environment (activity in V1, TO, AT) or about actions currently being performed (activity in M1$_\mathrm{L}$, PM$_\mathrm{L}$, PF$_\mathrm{L}$). Numbers indicate Brodmann Areas (BAs). (B) Schematic illustration of the 12 modelled

areas and between-area connections implemented (shown as bidirectional arrows). The colors indicate the correspondence between cortical and model areas. Thick and thin arrows indicate links already implemented in previous mean-field versions of the architecture and newly added ones, respectively. Arrow color discriminates "next-neighbour" connections (in black), linking cortically adjacent areas, from "jumping" ones (in purple), between non adjacent cortical areas. See main text for the neuroanatomical evidence used to determine the model's connectivity structure. (C) Schematic illustration of connectivity between 3 areas of the model. Each area consists of two layers (or banks) of 25x25 excitatory (upper) and inhibitory (lower) integrate-and-fire cells exhibiting neuronal fatigue. Between-area connections (black and purple) are sparse, random and topographic. (D) Neuron-level connectivity of one of the 7,500 single excitatory neural elements modelled (labelled "*e*"). Within-area excitatory links (in grey) to and from "cell" *e* are random and sparse, and limited to a local (19x19) neighbourhood of neural elements (area shaded in light-blue). Lateral inhibition between *e* and neighbouring excitatory elements is realised as follows: the underlying cell '*i*' inhibits *e* in proportion to the total excitatory input it receives from the 5x5 neighbourhood (darker-blue shaded area); by means of analogous connections (not depicted), *e* inhibits all of its neighbours.

Simulating learning of meaningful words

Twelve different instances of randomly initialised networks having the structure described above were implemented. Initially, each network was in a “naïve” state, in which all synaptic links (both within and between areas) connecting pairs of excitatory cells were established at random, as were their synaptic weights. Word learning and semantic grounding were then simulated by means of repeated learning trials, involving concomitant stimulation of the primary areas of the network.More precisely, the learning of six object- and six action-related words was simulated. To teach the model an object-related “word”, its primary areas A1, M1i, and V1 were repeatedly confronted with a triplet of pre-defined activation patterns. An activation pattern was simply a set of 19 randomly chosen cells (approximately 3% of the total 25-by-25 cells in one area). This was intended to reproduce a grounded learning situation in which words that are used to speak about visually perceivable objects are acquired via active usage (concomitant activity in A1 and M1i) in presence of the referent object (pattern in V1) (Harnad, 1990; Vouloumanos & Werker, 2009). Similarly, acquisition of an action-related word was simulated by repeated stimulation of areas A1, M1i, and $M1_L$, mimicking a situation in which the learning child uses the novel lexical item while executing the corresponding action (Tomasello & Kruger, 1992). Each of the 12 “*sensorimotor*” patterns was presented repeatedly in 3,000 learning trials, resulting in a total of 36,000 (randomly ordered) trials. Each of the 12 network instances was subjected to the same training procedure, using 12 different sets of (six object- and six action-related) sensorimotor “word” patterns, each pattern being repeatedly presented in 3000 learning trials. The training procedure is identical to that described in (Garagnani & Pulvermüller, 2016) – the reader is referred to Section “Simulating semantic symbol grounding” in that publication for more details.

Data collection & analysis

Simulated responses to words and pseudowords

After training, the network dynamics (responses to “word” and “pseudoword” patterns – see Section *Simulated responses to words and pseudowords* below – as a function of time) were recorded. The responses were collected separately for the 12 network instances, for each of the 12 areas, and, in case of word stimuli, for each semantic category (action- and object-related words). Each trained network was confronted with an activation pattern to area A1 for 500 msec (= 1000 simulation time-steps), simulating perception of a speech sound. The stimulus was either one of the "familiar", learned word patterns, or an "unfamiliar", untrained pseudoword pattern. Pseudoword patterns were built by randomly recombining sub-parts of the word patterns used for the training. More precisely, for each network, the "auditory" component of each word pattern (presented to area A1 during training) was divided into 25 smaller parts, consisting of 5-by-5 squares of 25 cells each; the "sub-squares" from the 12 word stimuli were then randomly recombined – preserving their original spatial position – to form 12 novel pseudoword stimuli (each containing 2 sub-squares from each of the original word patterns)[6].

Each testing trial started with a global network reset, whereby the membrane potential of all excitatory and inhibitory cells was set to 0. An interval of 1.5 sec (equivalent to 3000 simulation-time steps) followed, during which no input was provided and the network's activity was driven by noise (simulating spontaneous baseline firing). The stimulus was then presented to area A1 for 500 msec, followed by noise again during an inter-stimulus interval of 1 sec (total trial length was 3 sec). Each stimulus was presented for 10 repeated trials, leading to a total of 240 testing trials (corresponding to 12 min "real time", or 1,440,000 simulation time-steps) per network. During each testing trial network activity (total number of spikes and sum of all excitatory cells' membrane potentials in each area at each simulation time-step) was recorded. In the remainder of this chapter, the network's responses in each testing trial (sum of all excitatory cell's membrane potentials in each area) are referred to as "simulated event-related potential" (S-ERP) responses.

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[6] Pseudoword patterns used only 24 of the 25 possible sub-squares of the 625-cell grid. Also note that pseudowords somehow belonged to both of the two semantic categories, as they were made up of a random mix of sub-squares taken from both "action" and "object" words.

Time-frequency and synchronisation analysis

To investigate presence, power, and synchrony of oscillatory activity in the network the dynamic responses were analysed using Morlet wavelet analysis (Herrmann, Grigutsch, & Busch, 2005b; Roach & Mathalon, 2008; Tallon-Baudry, Bertrand, Delpuech, & Permier, 1997). More precisely, single-trial S-ERPs from each network area were convolved with a six-cycle Morlet wavelet (number of cycles c=6; wavelet length m=3; normalisation factor $A = \sigma_t^{-1/2} \pi^{-1/4}$) in 1 Hz and 10 msec bins from 4 to 100 Hz on the whole trial length (3s). The resulting single-trial total spectral power was then averaged across trials and networks, separately for pseudoword and word items, and (when appropriate) for semantic category (object- and action-related word). The same Morlet wavelet time-frequency decomposition was applied also to each network's averaged S-ERPs (obtained as described in Sec. 2.4.1), thus resulting in an estimate of the evoked spectral power (time- and phase-locked). An estimate of the induced spectral power (time-locked but not phase-locked) was then obtained by subtracting the evoked power from the averaged total power (David, Kilner, & Friston, 2006; Roach & Mathalon, 2008; Tallon-Baudry & Bertrand, 1999) in each condition. Baseline correction was performed by subtracting average activity between -500 and -100 msec (Roach & Mathalon, 2008).

To quantify the degree of between-area synchrony in the different conditions the coherence of the single trials' complex wavelet coefficients was examined; this measure is commonly taken as an index of the synchronous activity between different recording sites (Bastos & Schoffelen, 2015; Herrmann et al., 2005b; Roach & Mathalon, 2008; Sankari, Adeli, & Adeli, 2012). More precisely, the coherence of the oscillatory activity between the articulatory motor area (M1i), at one "end" of the network, and the primary visual (V1) and dorsal motor ($M1_L$) areas, at the other "end", was calculated separately for each word category and network instance, and averaged across the 12 networks. Coherence between M1i (used as seed channel) and primary areas V1, $M1_L$ was expected to differ depending on the semantic category (action- vs. object-related items) of the word stimulus. For the above processing steps the Fieldtrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) for Matlab (The Mathworks, Natick, MA, USA) was used.

Statistical analysis

In order to compare spectral power induced in the network by word and pseudoword stimuli, a two-tailed cluster-based permutation statistics with 1000 permutations and a t-test for dependent samples as thresholding statistics was carried out across all 12 areas and all 10-msec time bins of the epoch (from -1.5 s to 1.5s) on the average spectral power in the *a priori* selected frequency range between 20 and 40 Hz. The cluster-based permutation procedure is a non-parametric statistical test that controls the false alarm rate due to multiple comparisons of multidimensional data and is widely used for analysing time-frequency data (Maris & Oostenveld, 2007). The analysis was performed using the Fieldtrip toolbox (Oostenveld et al., 2011) for Matlab (The Mathworks, Natick, MA, USA).

4.3. Results

The training of the network led to the spontaneous formation of cell assembly circuits analogous to those obtained in previous (non-spiking) versions of the architecture (Garagnani & Pulvermüller, 2016; Tomasello et al., 2016), that is, sets of strongly and reciprocally connected cells linking together correlated patterns of "sensorimotor" activity. Visual observation of the network responses during presentation of learnt "word" and novel "pseudoword" items to the model correlate of primary auditory cortex indicated that both types of stimuli induced oscillatory phenomena, manifest in the form of "pulses" or waves of activity propagating across the network. Quantitative analysis of the recorded simulated responses confirmed this observation, but also revealed strong differences between the responses in the two conditions. Figure 4.2 reports the induced power in response to word and pseudoword presentation. The plots show a clear difference between the two conditions, particularly evident in the lower gamma band (25-30 Hz). Results of the statistical analysis fully confirmed this: the cluster-based permutation test comparing word vs. pseudoword responses in the 20-40 Hz frequency range revealed a significant difference between the two conditions (p=.0001). The positive cluster indicating higher spectral power for words than pseudowords extended over all areas and over the interval from -50 to 550 msec, corresponding to stimulus duration (considering the minimal time uncertainty intrinsic to time-frequency decomposition).

As the observed changes in (average) spectral power could be explained by changes in either the degree of synchronization of the signals across different trials or in the magnitude of the oscillations (or both) (Roach & Mathalon, 2008), in order to estimate whether word and pseudoword stimuli induced different magnitude oscillations an additional analysis was carried out on the peak membrane potential value reached (within an area) during the 50-to-500 msec interval of each trial, averaged across trials and network areas separately for the two conditions. A paired-sample *t*-test on these data confirmed that words exhibited larger peak amplitude responses than pseudowords (t_{11}=4.3, *p*=.001).

Figure 4.3 shows induced spectral power for the two semantic categories (action- and object-related words) in the different network areas. The time-frequency decomposition reveals topographically distinct spectral responses in the six extrasylvian areas (top lines of each diagram in Panel A) for the two word categories, particularly evident in the two "hub" areas (AT, PF_L). By contrast, the patterns in the six perisylvian areas (bottom lines) do not appear to exhibit between-category differences.

Figure 4.4 reports results of the coherence analysis performed on the oscillatory responses from three of the 12 network areas during simulated word recognition processes (data plotted in Fig. 4.3B). More precisely, the degree of synchrony between oscillations in area M1i and either primary visual (V1, left) or primary motor ($M1_L$, Right) areas induced by presentation of learned, meaningful object- and action-related words to area A1 is plotted as a function of time. Note the category specific double dissociation of synchronous oscillations exhibited by even "distant" (i.e., more than 1 synaptic step away) network areas.

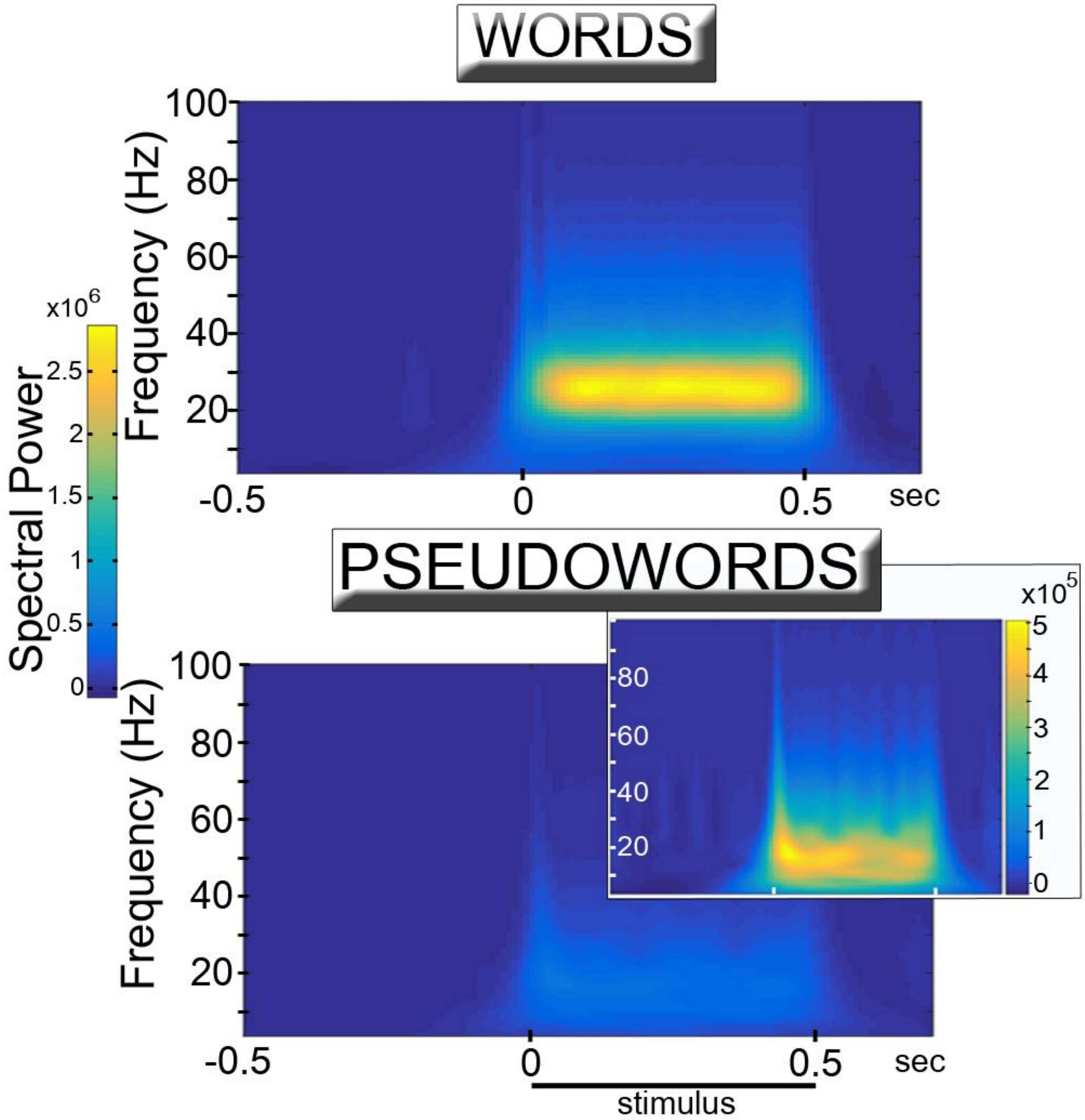

Figure 4.2. Simulated high-frequency responses to familiar, meaningful words **(Top)** and unknown, meaningless pseudowords **(Bottom & Inset)** items. The diagrams plot induced power (averaged across 12 network areas and 12 network instances) of the network's event-related responses (see Fig. 3) in the different frequency bands as a function of time. Learned, familiar word patterns induce strong oscillatory responses in the lower gamma band (25 to 30 Hz) during stimulus presentation. Unknown pseudoword stimuli appear to induce significantly weaker high frequency spectral responses. Adequate rescaling of the diagram plotting pseudoword responses **(Inset)** uncovers the presence of (smaller amplitude) oscillatory phenomena which, however, appear to peak at somewhat lower (~20 Hz) frequencies.

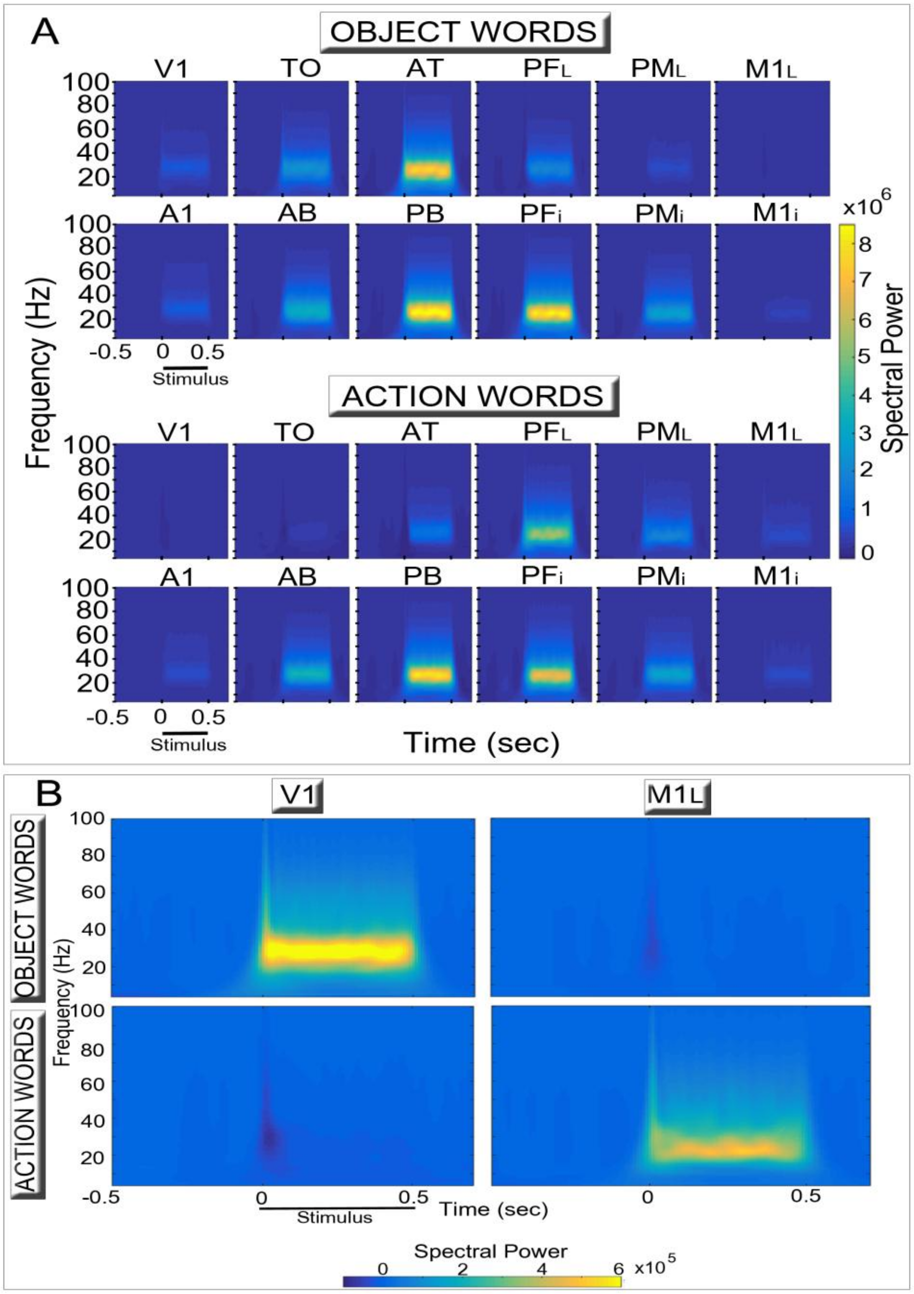

Figure 4.3. Network oscillatory responses during presentation of familiar object- (**Top row** in each diagram) and action-related (**Bottom row**) words. **Panel A:** for each area, induced spectral power of the simulated event-related responses is plotted for the different frequency bands and two conditions as a function of time. **Panel B**: a rescaled version of Panel A, plotting only data from the two primary extrasylvian areas (V1, $M1_L$). During presentation of a stimulus to area A1, both word categories induced high-frequency oscillatory activity peaking between 25 and 30 Hz (in line with the across-area averages shown in Fig. 4.2, top plot) which appear stronger in the central areas (AT, PF_L, PB, PF_i) (Panel A). Note the double dissociated responses exhibited by the extrasylvian areas (V1, TO, AT, PF_L, PM_L, $M1_L$). In particular, category-specific oscillations emerge in primary visual and motor areas (Panel B), with the former (V1) selectively responding to object-related words and the latter ($M1_L$) to action-related ones. Also note the presence of oscillatory responses at frequencies higher than 30Hz.

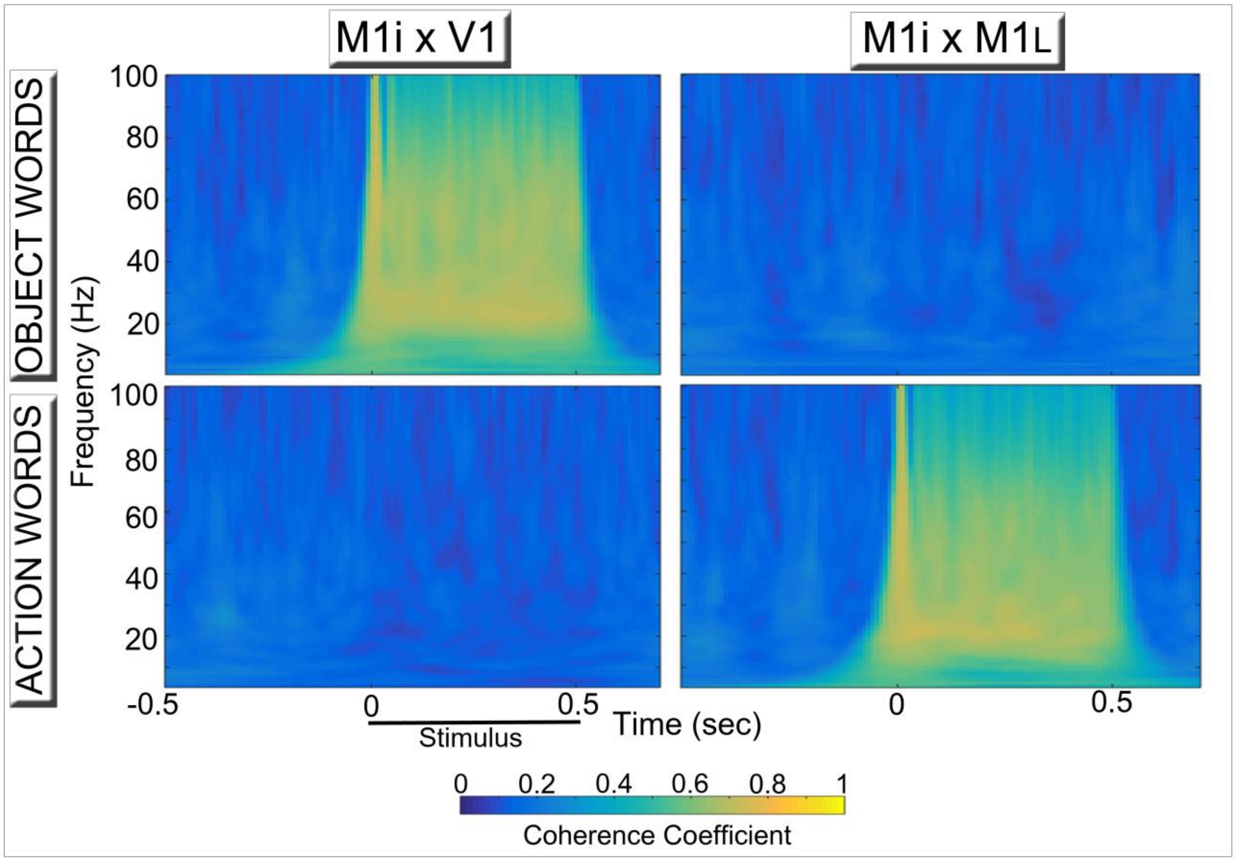

Figure 4.4 Synchronous activity in primary visual **(Left)** and primary motor **(Right)** areas induced by simulated recognition of spoken words grounded in the context of visual perception **(Top)** and action execution **(Bottom)**. Coherence coefficients between oscillatory responses in area M1i (where CA-circuit parts conveying model correlates of "articulatory" information are reactivated) and primary visual (V1, Left) and motor ($M1_L$, Right) areas (where simulated "perception" and "action" patterns of activation, respectively, are stored) during presentation of object- and action-related words to area A1 are plotted for the different frequency bands as a function of time. The synchronous activity reflects the periodic spreading of activity waves within stimulus-specific CA circuits (see Fig. 2, top plot), which link up phonological patterns in "auditory-articulatory" areas (A1, M1i) with "semantic" information coming from the model's sensory (V1) or motor ($M1_L$) systems. Note the clear double dissociation, whereby "articulatory" areas show a high degree of synchronisation with "visual" – but not with "motor" – areas during presentation of words with object-related meaning (Top diagrams) and action-related words exhibit the opposite pattern (Bottom diagrams), mirroring the spectral data shown in Fig. 3.B.

4.4. Discussion

A biologically realistic, spiking neural-network architecture closely replicating anatomical connectivity and cortical features of primary, secondary and higher-association areas in the frontal, temporal and occipital lobes of the human brain, was used to investigate the neural mechanisms underlying differential oscillatory responses to meaningful action- and object-related words and novel, senseless pseudowords. As a result of the simulated process of word learning, distributed, stimulus-specific cell-assembly circuits emerged, binding phonological (acoustic-articulatory) patterns in perisylvian areas with co-occurring semantic information coming from the sensory and motor (extrasylvian) systems. Crucially, after cell-assembly circuit emergence, the presentation of a learned "word" stimulus to the model correlate of primary auditory cortex (area A1) induced coherent oscillatory activity in the network within the lower gamma band (25-30 Hz), which was manifest as periodic "pulses" (spike bursts) of activation propagating within the cell-assembly circuit specific to that stimulus (see Fig. 4.2-4.3 and Fig. 4.5). By contrast, presentation of a novel, unfamiliar "pseudoword" pattern led to significantly smaller-amplitude oscillatory responses. These findings are consistent with experimental results reporting larger gamma band responses to words than pseudowords (Krause et al., 1998; Lutzenberger, Pulvermüller, & Birbaumer, 1994; Lutzenberger, Pulvermüller, Elbert, & Birbaumer, 1994; Mainy et al., 2008; Pulvermüller, Eulitz, et al., 1996; Pulvermüller et al., 1994). Furthermore, the cortical topography of stimulus-induced oscillatory patterns exhibited clear dissociations between semantic word categories in terms of both local spectral power (Figure 4.3) and inter-area coherence (Figure 4.4), again in agreement with some pre-existing experimental reports (Pulvermüller, Lutzenberger, & Preissl, 1999; Pulvermüller, Preissl, et al., 1996; Weiss & Mueller, 2013). These results, documenting category-specific spreading of activity within the stimulated CA circuits, provide a neuromechanistic account of action- and object-related word learning and recognition in the brain, as discussed below in light of neurophysiological evidence.

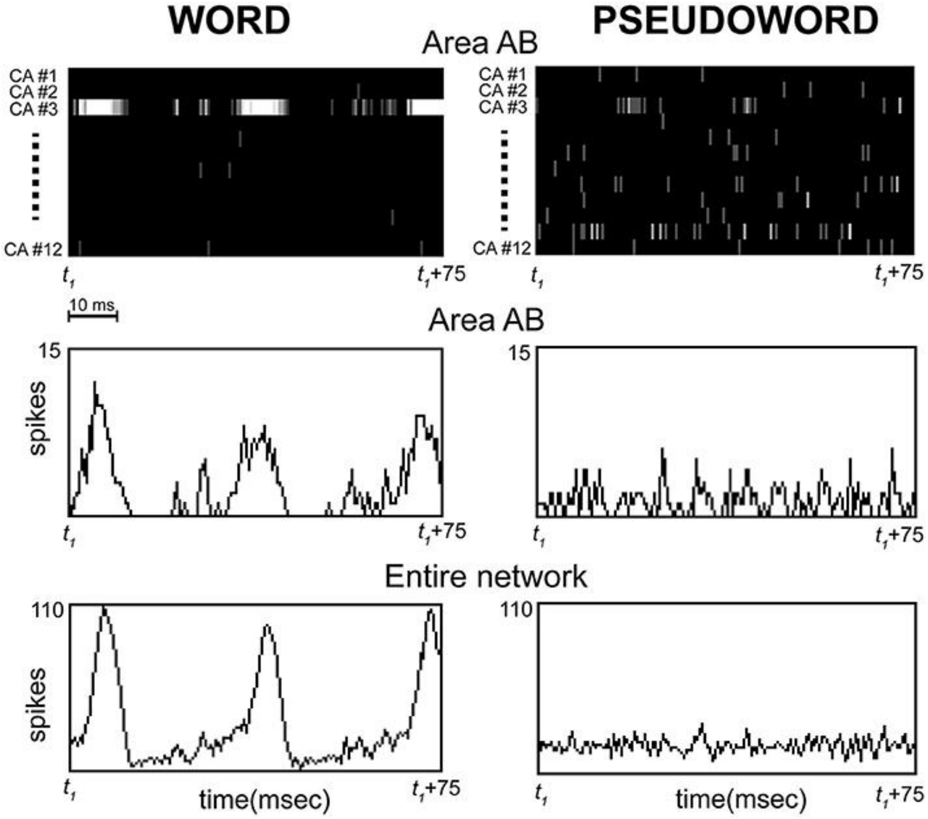

Figure 4.5. Representative example of simulated spiking responses over a 75msec interval sampled during continuous stimulation of area A1 with one of the learned word (Left) or “unknown” pseudoword (Right) patterns. The initial time point of the interval (*t*$_1$) does not represent stimulus onset, but an arbitrary time point chosen after the network had reached the “steady state”. Top: CA-specific raster plots showing spiking activity within each of the 12 cell assemblies (one for each line, labelled CA#1, … CA#12) in a representative network area (AB) are reported for the two conditions as a function of time; spikes are depicted as vertical lines on the black background (brightness indicates number of spikes per time bin). Middle: histograms plotting the total number of spikes per time bin in area AB for the two conditions as a function of time. Bottom: as Middle, but the histograms plot the total number of spikes within the entire network. Note (Left) the strong oscillatory activity (spike waves of approximately 30ms period) emerging selectively within CA-circuit #3 during stimulation with the corresponding word pattern, and (Right) the absence of such strong responses during pseudoword presentation, which is characterised instead by similar firing rates across all CA circuits and irregular, “out-of-synch” activity peaks (e.g., see CA#3 and CA#11). Also note the synchrony between the oscillations occurring in all network areas during word stimulation, suggested by the alignment between the peaks of the spike waves in the histograms for area AB (Middle-left) and entire network (Bottom-left). Time bins were 0.5 msec.

Mechanisms underlying the enhancement of the simulated high-frequency responses to words vs. pseudowords

In order to understand the model mechanisms that led to the observed result, the network's dynamic behaviour was inspected directly during stimulation. This revealed that, unlike words, pseudoword stimuli did not induce activation specifically within a *single* CA circuit, but, instead, partial co-activation of *many* cell-assembly circuits, within which smaller-amplitude[7] waves of activity propagated in a random, "incoherent" manner (see Fig. 5). To understand why this is so, note that each pseudoword pattern was built by randomly combining smaller sub-parts taken from all of the "learnt" word patterns; therefore, presentation of a pseudoword stimulated equally (on average) all word circuits at once, albeit to a much smaller extent (~1/12) than the amount a word pattern conveys to a single CA. The presence of regulatory mechanisms in the network (i.e., area-specific inhibition) leads the simultaneously stimulated circuits to inhibit each other; this reciprocal suppression (or "competition") has two main effects: first, smaller, sub-threshold waves of activity occur within each circuit, on average; second, and crucially, the mutually inhibitory interactions continuously at work between the competing CA circuits cause *anti-phasic* activity waves within them, i.e., *out-of-synch* spike bursts. As a result, the oscillations within different circuits tend to "cancel" each other out, leading, on average, to smaller-amplitude network responses (note the "flatter" profile of the histograms on the right-hand side of Figure 4.5).

By contrast, presentation of a learnt word pattern conveys the full amount of sensory input into neurons that belong to a single – and, hence, "non-competing" – CA circuit; this induces above-threshold activity and thus periodic circuit ignitions, manifest as synchronous bursts (or "waves") of spikes spreading within the entire circuit and network (Figure 4.5, Left). To sum up: a word stimulus conveys above-threshold activity within a single cell-assembly, inducing large-scale synchronous oscillations within it at its spontaneous ("resonance") frequency; by

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[7] This is confirmed by the analysis of the within-trial S-ERP peaks, see Section 4.3, Results.

contrast, pseudoword stimulation induces smaller and “out-of-phase” activity waves within competing CA circuits, resulting in overall weaker spectral responses.

This result is consistent with previous results, in which differences in neurophysiological responses (ERPs) to word and pseudoword items were replicated and explained (Garagnani et al., 2008). Such simulations showed that, in presence of sufficiently high levels of area-specific (global) inhibition (the model correlate of “low attention”), network responses to familiar, learned “words” are larger than to novel, unknown “pseudoword” stimuli; this was a consequence of the competitive interactions (mediated by area-specific inhibitory loops) occurring between the different CA circuits concomitantly (but only partially) activated by a pseudoword. In the present simulations, relatively high levels of baseline noise (simulating spontaneous neuronal firing) produce similarly strong amounts of global inhibition.Closer inspection of the results of the time-frequency analysis of the S-ERP data reveals the presence of another difference, namely, in the spectral profile of the responses: while word presentation elicits consistent, strong oscillations around 25-30 Hz during stimulus presentation, the pseudoword-induced responses exhibit a somewhat “irregular” spectral profile, with power peaks mostly below 20 Hz (see Figure 4.2, Inset). One can hypothesise that the above-mentioned competitive interactions may also underlie this “shift” towards lower-frequencies: in fact, mutual inhibition between co-activated CA circuits likely induces not only overall smaller responses but also small “delays” in the accumulation and propagation of activity within the CA circuits, leading to longer time intervals between the periodic peaks of activity, and, hence, to oscillations having generally longer wavelength. The fact that the power of the induced oscillations should peak at lower frequencies for pseudowords than for words is a novel prediction of the model; experimental data confirming this prediction would therefore provide strong evidence in support of the present mechanistic model.

Increased spectral power and long-range synchronization during word recognition

Spectral power

During presentation of a word stimulus the network exhibited substantial increase in spectral power peaking at around 25-30 Hz (see Figure 4.2) which, as revealed by Fig. 4, had category-specific topographic profile (as predictable from the double dissociations shown by the data plotted in Figure 4.3). These results are remarkably in line with some of the existing neurophysiological data. In particular, analogous double dissociations in high-frequency spectral power in occipital (visual) and central (motor) recording sites had been found for (visually presented) nouns and verbs having strong visual and motor semantic associations, respectively (Pulvermüller et al., 1999; Pulvermüller, Preissl, et al., 1996). As nouns and verbs differ not only in action-relatedness but also in lexical category, these results were prone to alternative interpretations, due to this confounding factor; more recent evidence (Moseley & Pulvermüller, 2014), however, has revealed differential brain activation to concrete nouns vs. concrete verbs, but not between abstract ones, corroborating the view that word meaning, rather than lexical category, is driving the observed topographical differences in brain responses (Moseley & Pulvermüller, 2014).

More generally, a large number of studies have documented increases in gamma-band response (GBR) amplitude during processing of meaningful words (compared to baseline) (e.g., Canolty et al., 2006; Edwards et al., 2010; Pei et al., 2011; Vignali, Himmelstoss, Hawelka, Richlan, & Hutzler, 2016; Wu et al., 2011). Most relevant to the present results, higher spectral power during processing of familiar items (words) vs. unfamiliar ones (pseudowords or non-words) has been found in English using MEG (Pulvermüller, Eulitz, et al., 1996) and ECoG (Canolty et al., 2007), in Finnish with EEG (Krause et al., 1998), in German with MEG (Eulitz et al., 1996), and in French, using intracortical recordings (Mainy et al., 2008), with remarkable consistency across languages, sensory modalities, and recording methods.

Long-range ("inter-area") synchronisation

The network simulations also revealed a high degree of synchronisation between model areas that are only indirectly connected (in particular, M1i – V1, top-left of Fig. 4, and M1i – $M1_L$, bottom-right of Fig. 4); crucially, such long-range synchrony depended on the semantic category, and was a by-product of the dynamic activation of circuits that included (or lacked) functional links between articulatory-phonological (M1i) and stimulus-specific semantic information in either primary motor ($M1_L$) or visual perceptual (V1) areas.

Experimentally, between- (inter-) -area synchronisation of oscillatory activity in non-adjacent cortical areas (here referred to as "long-range" synchronisation) has been widely documented in different sensory modalities and during different cognitive tasks using both invasive and non-invasive methods – see (Buzsaki & Wang, 2012; Harris & Gordon, 2015; Kaiser & Lutzenberger, 2003; Varela et al., 2001; Womelsdorf et al., 2007) for reviews. In particular, studies in the language domain found changes in long-range cortical synchronization during lexico-semantic and syntactic processing (Bastiaansen & Hagoort, 2006; Mellem, Friedman, & Medvedev, 2013; Supp et al., 2004; Weiss & Mueller, 2003; Weiss & Mueller, 2013; Weiss et al., 2005). Most relevant here is the recent work by Weiss and Müller (2013), who analysed oscillatory neurophysiological responses to concrete and abstract spoken words placed in semantically congruent and incongruent contexts. The authors found that, in incongruent sentences, lower-range (29-34 Hz) gamma band coherence between frontal and posterior recording sites was higher for concrete than for abstract items, interpreting this difference as indexing presence and reactivation of lexical-semantic circuits widely distributed over sensory and motor cortices (Weiss & Mueller, 2013). It should be noted, however, that coherence as measured at scalp level cannot be unequivocally attributed to synchronous oscillatory activity in distinct brain sources, due to the presence of possible volume conduction artefacts (Bastos & Schoffelen, 2015; Guevara et al., 2005; Trujillo, Peterson, Kaszniak, & Allen, 2005). Thus, in order to adequately test the prediction emerging from the present simulation results (in particular, Fig. 4), i.e., that word meaning comprehension processes are grounded in primary areas in a category specific manner, further studies of language-induced synchronous oscillations (either by means of intracranial recordings in patients or in source space) are desirable, potentially adopting paradigms successfully used in the past to reveal brain correlates of category specific semantic activations (Carota, Moseley, & Pulvermüller, 2012; Moseley, Carota, Hauk, Mohr, & Pulvermüller, 2012).

High-frequency cortical responses and long-range synchronisation in non-linguistic domains

As the neuroscientific principles (in particular, Hebbian learning) underlying the emergence of word-related memory circuits in the perisylvian areas are putatively at work in all other parts of the cortex, this account is consistent with experimental evidence showing the emergence of similar differences in high-frequency responses to familiar, well-learned vs. unknown, unrecognizable items also in other modalities, and predicts the presence (or absence) of analogous CA circuits there for the commonly occurring percepts. Indeed, different types of gamma oscillations have been documented not only in the auditory, but also visual, olfactory and somatosensory modalities, as well as during motor tasks, of both humans and animals (Cheyne, 2013; Engel & Singer, 2001; Tallon-Baudry & Bertrand, 1999). In the visual domain, earlier work on basic stimuli, investigating GBRs to coherently (i.e. parallel) vs. incoherently moving bars (Engel, Konig, Kreiter, & Singer, 1991; Engel, Kreiter, König, & Singer, 1991; Gray, Konig, Engel, & Singer, 1989; Gray & Singer, 1989) in animals was closely followed by cognitive investigations, with real object pictures eliciting greater GBRs than pictures of unrecognizable, fragmented or scrambled objects or faces (Bertrand et al., 2013; Craddock et al., 2015; Gao et al., 2013; Gruber et al., 2002; Hassler et al., 2011; Henson et al., 2009; Tallon-Baudry et al., 1996). Although Yuval-Greenberg and colleagues (Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008) showed that induced gamma-band activity (iGBA) in neurophysiological data can be contaminated by artifacts originating from miniature saccades or muscle activity, it should be noted that: (1) several of these results can hardly be attributed to effects of microsaccades, as, for example, these studies controlled for the physical features of the stimuli (Gruber et al., 2002), presented stimuli tachistoscopically so that eye movements were discouraged or excluded muscle artifacts based on EMG recordings (Pulvermüller, Birbaumer, Lutzenberger, & Mohr, 1997), or used intracortical recording methods (or magnetoencephalography, MEG) (Bertrand et al., 2013; Gao et al., 2013), which are minimally affected by small eye artefacts; (2) some evidence suggests that microsaccades actually decrease when looking at a coherent stimulus as compared to an incoherent one (Makin et al., 2011); and (3) the use of artefact-removing methods such as independent component analysis and beamforming (Craddock, Martinovic, & Muller, 2016; Keren, Yuval-Greenberg, & Deouell, 2010) enables identifying iGBA activity increases in the signal even after removal of miniature-saccade effects (Craddock et al., 2015; Hassler et al., 2011; Hassler, Friese, Martens, Trujillo-Barreto, & Gruber, 2013).

The results that reduced synchronization in the olfactory system can impair odour discrimination (Martin & Ravel, 2014; Stopfer, Bhagavan, Smith, & Laurent, 1997) and that modulation of both gamma and beta responses are linked with changes induced by olfactory learning (Martin, Gervais, Hugues, Messaoudi, & Ravel, 2004; Ravel et al., 2003) also constitute further pieces of evidence in support of the hypothesis mentioned at the beginning, i.e., that CA circuits for commonly occurring percepts may emerge in the cortex in different modalities and cognitive domains.

The results plotted in Figure 4.5 (in particular, middle and bottom-left diagrams) suggest that, during word presentation, the oscillations in the different model areas exhibit an almost zero time-lag synchronization. The emergence of *quasi*-zero phase-lag in the simulations is interesting, but not entirely surprising: previous work using multi-area spiking networks has linked this phenomenon, for example, to local inhibitory interactions (Traub, Whittington, Stanford, & Jefferys, 1996) or global regulatory loops (Vicente, Gollo, Mirasso, Fischer, & Pipa, 2008), both of which are implemented here. It is known, however, that modelling realistic axonal transmission delays may also prevent zero-lag synchronisation, or even induce anti-phase interactions (Knoblauch & Palm, 2002; Knoblauch & Sommer, 2003); as the present model does not implement conduction delays, any strong prediction about the phase lag based on the results presented here should be taken with caution (Viriyopase, Bojak, Zeitler, & Gielen, 2012). On the other hand, experimental evidence for zero time-lag synchronization across distant cortical regions (including interhemispheric areas) and sensory modalities during different tasks has been observed, using invasive recordings in both humans – typically from epileptic patients in surgical settings (Lachaux et al., 2005; e.g., Rodriguez et al., 1999) – and animals, in the beta (Bressler, Coppola, & Nakamura, 1993; Roelfsema, Engel, Konig, & Singer, 1997; Witham, Wang, & Baker, 2007) and gamma band (Engel, Kreiter, et al., 1991; Gregoriou, Gotts, Zhou, & Desimone, 2009; Roelfsema et al., 1997; von Stein, Chiang, & Konig, 2000). It should be emphasised, however, that the role of synchrony and neural-population responses in cognition is still object of ongoing debate (cf. Gilad & Slovin, 2015; Martin & von der Heydt, 2015).

Conclusions

Time-frequency analysis of oscillatory activity in a neuroanatomically realistic neural-network model in response to simulated familiar words and to novel, unknown pseudowords showed larger high-frequency activity for the former than the latter. This result can be explained on the basis of spontaneous emergence and competitive interactions of cell-assembly circuits for words. The model links the different spectral responses to corresponding differential oscillatory dynamics of underlying large-scale neuronal populations, with periodic “bursts” of spikes occurring within a single, stimulus-specific circuit during presentation of a well-learnt, meaningful word, and absence thereof during pseudoword input (characterised, instead, by “out-of-phase” and smaller amplitude responses within multiple competing CA circuits). In addition, the model replicates and extends previous results obtained with a simpler, graded-response version of the architecture, demonstrating spontaneous emergence of stimulus-specific cell-assembly circuits by means of a novel, spike-driven Hebbian plasticity rule at work within a more accurate neuroanatomical structure. Finally, coherence analysis of the simulated neurophysiological responses reveals the presence of double dissociations in the category specific patterns of synchronous oscillations observed in distant cortical areas, in line with existing experimental results. Linking cellular-level mechanisms and neuronal-population behaviour with cognitive function, this study contributes to bridging the gap between experimental data and scientific theory by means of a computational architecture based entirely on neurobiologically realistic principles, hence providing further evidence in support of an account of acquisition of form-meaning pairs and semantic learning by way of biological principles of functioning of the human cortex.

5. Discussion

5.1. Summary of results

Chapter 2 – Study 1

Construction processing in the healthy human brain was tested using the MMN, with a specific focus on respective roles of storage-related and combinatorial mechanisms. MMN brain responses indexing processing of constructions – which were either well-formed, or contained unstored items – making them similar to jabberwocky speech, or violated combinatorial morphosyntactic rules, or included both kinds of violation and were presented in a fully balanced orthogonal design – showed a very early interaction of the two types of violation over time. This interaction between storage-related and combinatorial properties unfolded between 70 and 210 ms after the critical construction-disambiguating syllable was made available. The MMNs to double violation strings were consistently smaller than those to well-formed constructions across the whole 70-210 ms interval, whereas storage-related and combinatorial single violations elicited initially smaller MMNs that increased towards the end of the interval reaching amplitudes comparable to the MMNs to well-formed phrases. These results indicate that the brain processed constructions by retrieving and combining information in a highly integrated fashion from very early on during language perception, i.e. within the first ca. 200 ms after the onset of the disambiguating syllable, and, crucially, were obtained in a highly controlled experimental design that ruled out concerns about undesired variability and uncontrolled context effects. This early interaction involving storage-related and combinatorial mechanisms has relevant implications for neurophysiological models of language processing, brain theory of language, and for constructionist linguistic approaches.

The results 1) question modular syntax-first cascaded processing and strongly support parallel models envisaging simultaneous, early, and interactive processing of whole-form stored constructions and combinatorial processes by which stored elements are being joint together; 2) match the predictions made on the basis of brain theories of cell assemblies as biological basis for language; 3) highlight the high degree of integration of the mechanisms for storage/retrieving and combination while stressing the need for distinguishing between these two types of mechanisms.

Chapter 3 – Study 2

Construction processing in chronic aphasic patients was tested using a passive MMN paradigm before and after intensive language therapy in order to examine brain correlates of therapy-induced language improvements. Two-word (pronoun-verb) constructions that were either well-combined, ill-combined, or contained a meaningless, unstored item (i.e. pseudoverb), were presented as critical deviant stimuli. The MMN responses to well-formed mini-constructions significantly increased over a 4 week therapy interval and a similar increase was found for morphosyntactically well-combined but pseudoword-including ‘jabberwocky’ constructions. By contrast, no changes across therapy emerged from the MMN responses to ill-combined constructions that included meaningful words but violated morphosyntactic agreement.

These results suggest that therapy-induced neuroplasticity of language networks can be interpreted in a constructionist framework and that language reorganisation is restricted to meaningful and potentially compositionally meaningful constructions, but is blocked or at least much more difficult to achieve for strings that violate basic principles of combination. Approaches to aphasia therapy may take into account this finding in the future by aiming at better methods addressing the brain’s combinatorial mechanisms.

Chapter 4 – Study 3

Oscillatory activity from modelled brain networks for language was examined during processing of simple stored constructions, i.e. words, vs unfamiliar items, i.e. pseudowords. The neural-network architecture was biologically realistic, both in terms of anatomical connectivity and of functional properties at neuronal level, and was preliminarily trained to simulate word-learning corresponding to the emergence of constructions by means of cognitive mechanisms as postulated in usage-based linguistic theories. The result of training was the emergence of distributed, stimulus-specific cell assembly circuits. After training, the presentation of learned simple constructions to the model induced in the network high-frequency (lower gamma band) oscillatory activity of the cell-assembly circuit specific to each stimulus. By contrast, unfamiliar non-learned stimulation patterns lead to significantly smaller-amplitude oscillatory responses. These results replicated very closely the findings from electrophysiological studies on healthy subjects reporting larger gamma band responses to words as opposed to pseudowords.

These results show that modelling the language neural networks following neurobiological realistic principles like hebbian associative learning allows for the replication of electrophysiological correlates of construction processing, thereby mechanistically linking the emergence of constructions (simple words in this instance) to the emergence of cell assemblies. Simultaneously, these simulations provide a first tentative model of some relevant neural processes possibly taking place during language learning and aphasia rehabilitation, although similar modelling of the emergence of combinatorial mechanisms still remains a target. Pairing electrophysiological techniques with computational modelling appears to be a promising approach to explore more complex aspects of construction processing in future research.

5.2. Significance for models of language processing and brain theory of language

Processing of constructions of different levels of complexity was tested with electrophysiological methods in the healthy, aphasic, and modelled human brain, and this section discusses the implication of the results of these investigations for neurophysiological models of language processing and for brain theories of language. As already explained in the Introduction, previous electrophysiological research on language processing has led to two different models of language comprehension, one dictating cascaded syntax-first processing and the other one envisaging early parallel assessment and integration of different kinds of linguistic information. Recent ERP/F research has indeed uncovered brain indices of storage-related lexico-semantic and combinatorial syntactic aspects of language in the same early time range (< 200) (see Section 1.2) thus indirectly suggesting parallel processing. The present electrophysiological investigation on storage/retrieval and combination of constructions above single word-level in the healthy brain (Chapter 2 – Study 1) tested the two processes at the same time in the same subjects in a fully controlled experimental paradigm and could therefore confirm that the two mechanisms are active in parallel at very early stages of language processing. Crucially the two mechanisms were found not only to run in parallel but also to interact with each other (see 2.3 and 2.4) matching the prediction formulated on the basis of the brain theory of language based on the emergence of cell assembly and making it hard to argue in favour of cascaded psycholinguistic models of language perception.

In terms of brain theory, the early interaction of storage-related and combinatorial mechanisms is consistent with a neurobiological account of language based on the emergence of cell assemblies, as proposed by Pulvermüller (Pulvermüller, 1999, 2001, 2002, 2010) and discussed in the Introduction (see Section 1.1). Specifically, the brain mechanism responsible for combination at the cellular level would be the emergence of discrete combinatorial neuronal assemblies (DCNAs) that are large ensembles of cell assemblies responsible for lexical storage and linked together by way of sequence-sensitive units. It is interesting to note that the emergence of the DCNAs has been demonstrated to incorporate not only purely syntax related aspects but also semantic ones (see Figure 1.2, panel B) (Pulvermüller & Knoblauch, 2009). This implies that different kinds of linguistic information would be processed by the same networks for language and not in a modular fashion as cascaded models assume. The early interactive processing shown by the results of Study 1 indeed supports the former view and questions the latter one, thus providing experimental support for the cell assembly theory of language. Crucial evidence in this direction comes also from Study 2 (Chapter 3), in which the MMN was used to examine changes in processing of constructions in aphasic patients during therapy. The cell-assembly theory of language predicts that therapy-induced neuroplasticity would occur through cell assembly consolidation and therefore stronger responses for constructions should follow therapy. This was found indeed for constructions that were either well-formed or well-combined, whose MMN responses significantly increased over therapy (see 3.3 and 3.4). Interestingly, combinatorially anomalous constructions did not show any increases. This bears relevance to a constructionist approach to language processing, as discussed in detail below in Section 5.3.

Focussing on storage-related aspects of construction processing, Study 3 adopted a different experimental approach. First, it examined construction processing in a computational model of the human brain entailing primary, secondary, and higher-association areas in the frontal, temporal, and occipital lobes. The architecture of the network was such that it encompassed anatomically accurate connectivity and physiologically accurate associative properties at the synaptic level, thus reproducing associative learning, and was trained to simulate construction/word learning. Second, electrophysiological methods were applied but, moving away from ERP techniques adopted in Study 1 and 2, the network responses in the testing phase were analysed with time-frequency analysis to uncover patterns of oscillatory activity. Oscillatory responses to stored linguistic items have already been investigated in healthy subjects, as discussed in the Introduction and in Chapter 4 (see Sections 1.1, 4.1, and 4.4) and higher power of oscillations in the gamma band indexes retrieval of stored items as opposed to novel unfamiliar ones. The results of Study 3 crucially replicated these findings, thus providing a mechanistic link between storage of linguistic information, i.e. constructions, and cell assembly formation. The model was pre-equipped with physiologically and anatomically realistic characteristic but not with cell assemblies that emerged spontaneously during learning and whose activity showed oscillations, like in actual human brains, during retrieval of constructions. This kind of mechanistic link has already been provided for ERPs data on language processing (see Introduction,1.1, and Garagnani et al., 2008) but was missing in regard to oscillatory activity and therefore Study 3 provides a further element in support of a coherent picture which binds together models of oscillations in perception, language processing, cell assemblies for language, and constructions.

In summary, the results from the experiments described in the present work indicate that language processing in the brain is a parallel interactive processing from the very early stages, that it can be explained with the emergence and consolidation of cell assemblies, and that combinatorial and storage-related mechanisms play fundamental roles in it.

5.3. Significance for linguistic theories and grounding of constructions in the brain

The results of the present work investigating electrophysiological correlates of construction processing have implications not only for brain theories but also for constructionist approaches to language. Constructions are pairs of form and meaning and the matching of the meaning with the specific form of a construction can be thought to depend on the storage/retrieval of symbolic representations, but also to rely upon combinatorial aspects, what has been called "compositionality of construction meaning" and is a core aspect of more complex and abstract constructions (see Section 1.1 and Kay & Michaelis, 2012). A constructionist approach allows to envisage early interaction of storage-related and combinatorial aspects in processing constructions above single-word level. Study 1 provided strong evidence in this sense coherently with such a theoretical framework. As extensively discussed in the Introduction (Sections, the traditional linguistic distinction between lexicon and syntax cannot be identified in full with storage-related and combinatorial processes, because combination can work below word-level and storage above it (see Figure 1.1); and indeed the majority of constructionist approaches smoothen in a way the former of the two dichotomies, considering lexicon and syntax as the two ends of a continuum instead of two completely separate entities (Pulvermüller et al., 2013), and some more extreme positions do not even see remarkable differences between the two processes (Croft, 2001, 2013; Tomasello, 2003). Formulating the issue of interactive processing in language comprehension in terms of storage-related and combinatorial processes in the brain, instead of lexicon and syntax, may then be more appropriate in order to investigate the brain foundations of constructions, since the two processes are thought to be necessarily involved in pairing the form with the meaning, especially for higher-order constructions. It has already been discussed in the previous Section (5.2) how Study 1 indeed demonstrated that these two types of processes, i.e. storage/retrieval and combination, occur at the same time and affect each other, but the same electrophysiological evidence also highlights the necessity to maintain a distinction between the two. As a matter of fact, the double-violation condition elicited a pattern of electrical activity that was significantly different from the well-formed constructions and from each of the two single violations, either combinatorial or storage-related, and was not due to linear summation of the latter two (see Figures 2.3, 2.4; and Sections 2.3, 2.4). This indicates that the brain indeed processes the two types of information in parallel and in an interactive fashion, but nevertheless as two different types of information.

Recovery of the language function shown by Study 2 was accompanied by the enhancement of MMN responses to constructions that were either well-formed or included an unstored item that was nevertheless compositionally correct, whereas this was not the case for the ill-combined ones. Therefore, a critical factor contributing to normalisation of electrophysiological correlates of language processing appears to be the context in which words and pseudowords are embedded. The pseudoword presented to the patients in Study 2 was morphosyntactically congruent with the preceding pronoun, so that the form of the complex two-word construction ("*ich leige*", *leige* being a pseudoword) was intact, thus allowing for integration of the *per se* meaningless item into the context of a one-place verb construction schema. Behavioural evidence shows that 'jabberwocky' constructions, i.e. sentences that include no content words but observe the combinatorial structure of the construction schema, prime verbs that semantically fit into the same construction schema (Johnson & Goldberg, 2013).

Similarly, the one-place 'jabberwocky' construction in Study 2 ("*ich leige*") might have semantically induced a certain degree of activity in the brain representations of meaningful verbs that occur regularly within this type of construction, that is one-place verbs such as, for instance: *leiden* ("to suffer"), *schlafen* ("to sleep"), etc.. The constructionist framework offers a unique vantage point to interpret these results (as discussed below in 5.4); at the same time the results support the idea of pairing of form and meaning above single word-level in complex constructions.

From a neurobiological perspective, the idea that a certain degree of semantic processing can be induced by 'jabberwocky' constructions through the activation of an abstract combinatorial-semantic construction schema sits well with mechanisms of emergence of brain representations of combinatorial schemata in the brain as shown by Pulvermüller and Knoblauch (Pulvermüller & Knoblauch, 2009) and discussed above (see 1.1, Neurobiology of combinatorial mechanisms, and 5.2). These combinatorial schemata would be implemented in the brain as discrete combinatorial neural assemblies (DCNAs) that provide not only syntactic but also semantic linkage, by way of plastic strengthening of synaptic connections due to frequency of co-occurrence, between smaller cell assemblies that represent single words. Such a mixed lexico-syntactic-semantic relevance of DCNAs also implies indirect strengthening of connections and clustering of words that are related in valency and semantics (see Figure 1.2). Therefore, brain activity induced by function words and phonemes building up morphosyntactically correct pseudoword could, in principle, induce a certain degree of activation of the neural representations of actual meaningful words that typically occur in the same combinatorial schema. Remarkably, the mixed syntactic-semantic value of DCNAs as representation of complex combinatorial language structures in the brain also leads to predict highly interactive combinatorial and storage-related processing, as it was clearly shown in Study 1. Therefore, the present results from both healthy and aphasic subjects provide support for a linguistic constructionist framework that encompasses highly intertwined combinatorial and storage-related processes for language.

Such interactive access and combination of stored items in the brain require highly coordinated activity of cell assemblies spread across distant cortical areas and this could be reflected in high-frequency oscillatory patterns. Study 3 indeed showed that construction processing in the brain is associated with high frequency oscillatory activity, and specifically that access to learned linguistic forms paired with meaning, i.e. constructions, induces a higher degree of such oscillatory activity than meaningless combinations of phonemes. Hence, the study object of the third chapter of the present work not only provides a mechanistic explanation for the emergence of construction, in the brain, confirming previous similar modelling work (Garagnani & Pulvermüller, 2011, 2013, 2016; Garagnani, Shtyrov, et al., 2009; Garagnani et al., 2007, 2008; Garagnani, Wennekers, et al., 2009; Pulvermüller & Garagnani, 2014; Tomasello et al., 2016), but also shows that such storage-related operations occur through high-frequency oscillatory patterns of neuronal activity.

Taken together, the results from the experiments presented here indicate that neurophysiological evidence on constructions processing can be biologically explained in the framework of the cell assembly theory of language and support the idea that storage-related and combinatorial mechanisms emerging by way of associative learning can indeed be the brain basis of constructions.

5.4. Significance for a constructionist approach to aphasia

It was discussed in the Sections 5.2 and 5.3 how the present work indicates that storage-related and combinatorial mechanisms can both contribute to the emergence of constructions in the brain by means of cell assembly formation, thus bringing together neuroscientific insights into language with constructionist linguistic approaches. A crucial aspect of such a multidisciplinary take on language processing is its potential relevance for a better understanding of language impairments, and specifically of post stroke aphasia, and therefore for a consequent improvement of therapeutic strategies. Indeed, as mentioned in the Introduction (see Section 1.3, *Neurobiology insights into language improve therapy of post stroke aphasia*), applying neurobiological insights to rehabilitation of aphasia has been shown to be a fruitful approach (Berthier et al., 2009; Berthier & Pulvermüller, 2011; Mohr et al., 2014; Pulvermüller & Berthier, 2008; Pulvermüller, Neininger, et al., 2001; Stahl et al., 2016) and neurophysiological tools like ERPs and the MMN are used for investigating treatment induced plasticity (MacGregor et al., 2015; Mohr et al., 2016; Pulvermüller, Hauk, et al., 2005). Adopting linguistic approaches to aphasia is not a new idea (Cornell, Fromkin, & Mauner, 1993; Grodzinsky, 1984, 1995; Thompson & Shapiro, 2005). Moreover, it has been recently suggested that a constructionist framework may provide a better account of the patterns of aphasic impairment spanning across lexicon, morphology, and syntax than traditional linguistic views (Duffield & Menn, 2014; Gibson, Sandberg, Fedorenko, Bergen, & Kiran, 2015). In this regard, the present work attempts at unifying neurobiological and constructionist approaches to language processing, and Study 2 in particular indicates that a constructionist framework not only may help in addressing patterns of linguistic impairment in aphasia as behaviourally measured, like the literature above mentioned suggests, but could also be beneficial in interpreting electrophysiological MMN correlates of recovery of the language function in patients undergoing intensive rehabilitation therapy.

As shown in Sections 2.4 and 5.3, the amplitude of MMN responses to combinatorially correct sentences increased over therapy regardless of the lexical status of their constituents, whereas MMN responses to morphosyntactically ill-combined sentences did not change across therapy. This pattern, that would be hard to interpret in a traditional linguistic framework, is consistent with a constructionist framework that predicts a strong mutual influence, i.e. an interaction, of combinatorial, also referred to as compositional (Duffield & Menn, 2014; Kay & Michaelis, 2012), properties of complex constructions on the access of their semantic content. In order to better illustrate how this is the case, it is necessary to examine the MMN changes to each condition in light of previous neurophysiological research on intensive aphasia therapy.

The therapy-related increase of the MMN in response to well-formed constructions – i.e. the ones containing actual verbs in agreement with the respective pronoun – replicated ERP results previously obtained with simpler constructions, that is to say single words (MacGregor et al., 2015; Mohr et al., 2016; Pulvermüller, Hauk, et al., 2005). Therefore, Study 2 not only was consistent with these previous experimental results but also extended the evidence on neurophysiological correlates of construction processing during treatment to the level of complex constructions over and above single words. Precisely this higher degree of combinatorial complexity of the constructions tested in Study 2 also explains the increase of the MMN amplitude to a pseudoword in the appropriate combinatorial morphosyntactic context (i.e. to "jabberwocky" constructions), as extensively discussed above in Section 5.3. Hence, the apparent contrast of this result with previous studies that did not find any therapy-induced change for pseudoword seems to be a direct consequence of the higher degree of complexity of the constructions used as stimuli in the present study as compared to the previous ones (MacGregor et al., 2015; Pulvermüller, Hauk, et al., 2005). Intensive aphasia therapy seems to be associated with improvement in construction processing as shown by the increase in brain activity in response to meaningful, even if partly, constructions.

Coherently, constructions whose combinatorial schema was violated did not induce increased brain activation after therapy than before it; once again this is with the idea that the combinatorial, or compositional, properties of constructions are tightly bound and interact with the retrieval of their content. It is important to remark that the ill-combined pronoun-verb sentence that did not show increase in MMN responses after therapy included words that, out of context, would have been expected to show enhanced responses associated with well-formed constructions. On the contrary, the combinatorial agreement violation may have hindered the access to the construction schema and, possibly, any neuroplastic changes with it.

While construction grammar appears to offer a fresh focus on the neurophysiology of language recovery in aphasia, an explanation of the pattern of results presented here would be difficult to find with a more traditional linguistic approach to words and rules (Chomsky, 1957; Pinker, 1997), which would not take into account the differences between combinatorial and storage-related processes on one hand, and grammar and syntax on the other hand. In a classic "words and rule" perspective, the neuroplastic change in response to linguistic structures above single morpheme-level would be interpreted exclusively in terms of morphological or syntactic rules and the traditional neurophysiological indexes of grammar processing show an increase in their amplitude in response to violations as compared to correct word and morpheme sequences (see 1.2, Cascaded processing and Parallel processing, and Gunter et al., 2000; Hahne & Friederici, 1999; Hasting et al., 2007; Neville et al., 1991; Shtyrov et al., 2003). Such a traditional linguistic approach to neurophysiology of language recovery in aphasia would then be unable to explain the concomitant increase in MMN to 'jabberwocky', pseudoword- or pseudo-morpheme-containing constructions and absence of increase in response to ill-combined complex constructions. As a matter of fact, the classic rules/words approach would be bound to interpret the MMN increase to jabberwocky strings as an improvement of rule-processing mechanisms (not of lexico-semantic, because jabberwocky sentencescontain meaningless items). But if an improvement in rule-processing systems had occurred thanks to the therapy, the MMN response to ungrammatical combinatorial violations should have also increased, and this was not the case. These two elements (improvement of rule-processing and absence of MMN increase for grammatical violations) are clearly at odds and therefore a traditional "words and rules" approach is not able of explaining the results.

On the contrary, a constructionist approach leads to the prediction of an increase of the MMN response to a consolidated abstract combinatorial-semantic construction schema and is consistent with the absence of increase for ill-combined strings, if one assumes that there is a lack of semantic access in ill-combined constructions. This is the case because construction grammars implies continuity and tight links between the combinatorial, or compositional, structure of a construction and access to its content (Duffield & Menn, 2014; Goldberg, 2006; Hoffmann, 2013) and therefore the combinatorial violation may hinder the access to construction schemata and their content. At the same time, the increased response to pseudoword-containing constructions is plausible because there is evidence of semantic links between jabberwocky and real sentences (Johnson & Goldberg, 2013).

In summary, a construction grammar framework appears to be helpful and more powerful than more traditional linguistic views in interpreting electrophysiological – and, more broadly, experimental – data on recovery of language in post stroke aphasia during intensive rehabilitation therapy.

5.5. Limitations and future perspectives

The present work addressed questions about construction processing in the healthy, aphasic, and simulated human brain – specifically if and when combinatorial and storage-related mechanisms interact during construction processing, how they affect the neurophysiology of construction processing as an index of language recovery in treated chronic post stroke aphasia, and if the access to construction schemas in the brain by way of cell assembly activation and oscillatory dynamics can be successfully simulated in biologically realistic computational models. On the one hand it appears that the results of this experimental investigation provided some, at least partly satisfactory, answers to the posed questions, on the other hand they raised a possibly equal if not greater number of additional questions and showed some limitations that must be addressed.

In order to investigate construction processing in the healthy and aphasic brain, MMN designs were used. While the MMN offers a number of advantages in neurophysiological linguistic research both in clinical and non-clinical settings – as extensively discussed in Sections 1.2, *Parallel processing* and 1.3, *The MMN in post stroke aphasia* – one can argue that, at the same time, it implies an unnatural degree of repetition of limited linguistic material, thus resulting in somewhat artificial experimental settings of limited ecological validity. The most obvious consideration in this regard is that any experimental setting will always affect the observed phenomenon. On a more subtle level, one must point out that many results that were first obtained thanks to the high degree of experimental control granted by the adoption of MMN paradigms have been replicated in studies using a larger number of stimuli and without any repetition. This suggests that the MMN was indeed the ideal tool to adopt in the present work in order to explore linguistic phenomena that require high experimental control of confounding factors, as it was the case of very early combinatorial and storage-related interaction Study 1 or construction processing in a clinical population in Study 2, but also that the results presented here need to be replicated in future studies adopting different paradigms with a more flexible trade-off between control and naturalness.

Study 1 showed a very early interaction of combinatorial and storage-related mechanisms in construction processing in healthy subjects, while Study 2 indirectly provided some evidence for the relevance of both factors in language recovery. Both studies seem to be unprecedented in the literature, the first one in addressing the interaction issue in terms of combination and storage and at very early latency thanks to the MMN, the second one in extending the MMN investigation of language recovery to complex construction above single-word level. These two studies provide the basis for future investigations directly testing combinatorial and storage-related mechanisms in patients suffering from post stroke aphasia. Moreover, it will be relevant to investigate in the future the brain dynamics related to processing of pseudowords in and out of larger, more complex constructions in the same patients before and after therapy.

As mentioned in the introduction and confirmed by the results of this work, shifting the perspective on neurophysiology of language processing from the traditional linguistic distinction between grammar and lexicon to the more construction-compatible one between combinatorial, or compositional, and storage-related properties appears to be beneficial in formulating hypotheses and interpreting results. From this vantage point, in particular some aspects of combinatorial processing that emerged from the present investigation have to be addressed in future research. First, although Study 1 showed a clear effect of combinatorial properties of the stimuli on the brain activity during their interaction with the storage-related mechanism, a clear index of the combinatorial mechanisms in isolation failed to emerge. Indeed, on the basis of previous MMN research on combinatorial processing – as discussed in Sections 1.1, *Neurobiology of combinatorial mechanisms*, and 1.2, *Parallel processing* – one would have expected a larger response to the ill-combined stimuli as compared to the well-formed ones. Instead, no significant differences emerged between the two conditions (Section 2.3, Figures 2.3 and 2.4). This may be related to the complex design, which was adopted in Study 1 for the first time and involved the repetition of the same four critical syllables across the eight stimuli (50%) that violated morphosyntactic agreement, in both the ill-combined and the double violation condition (see Table 2.1), thus possibly inducing a degree of adaptation in the otherwise fully igniting, unprimed cell assemblies. However it will be of relevance to provide a satisfactory neurobiological explanation for it in future investigations.

In post stroke chronic aphasic patients, therapy induced somewhat in contrast with previous literature an increase of MMN responses to combinatorially correct but pseudoword including constructions and no changes for wrongly combined but fully lexical ones (see Sections, 3.3, 3.4, 3.5, 5.3, and 5.4). Also in this case the relevance of the combinatorial aspects of construction processing clearly emerged. However, future studies are necessary to replicate and further explore the lack of change for the combinatorial violation, in order to gain a precise biological account of this phenomenon. In this direction it would be beneficial to perform similar experimental investigations on larger groups of patients.

Study 3 showed that access to constructions can be operated by way of cell assemblies and it is associated with their oscillatory dynamics. Remarkably, synchronisation of high frequency beta and gamma oscillatory activity of representations of unitary stored items appears to be involved in binding above single word level, that is to say in combinatorial processes, as oscillatory dynamics in these frequency bands seem to reflect language processing at sentence-level (Bastiaansen & Hagoort, 2006, 2015; Bastiaansen et al., 2010; Lewis et al., 2015; Weiss & Mueller, 2003; Weiss & Mueller, 2013; Weiss et al., 2005). Extending the computational modelling above single-word, simple constructions is necessary in order to simulate combinatorial processes and oscillations in the gamma/beta bands, and therefore developing such combination-capable models and analysing their patterns of oscillatory activity is a future step in the computational investigation of construction processing and storage-combination interactions.

Finally, in light of the results here presented, unifying the computational and clinical approach under the constructionist theoretical framework and modelling the aphasic lesioned brain for testing therein combination and storage/retrieval of simple and complex constructions appears to be a fruitful strategy in order to further both the understanding of the disease and the efficacy of the treatment.

5.6. Conclusions

The present work indicates that the language faculty involves retrieving and combining stored linguistic representations of various levels of complexity by way of spatio-temporal patterns of activation of cell assembly networks. The two processes, albeit distinct, are tightly interwoven and occur simultaneously very early during language perception and understanding, interacting with each other. Rehabilitation-induced language recovery in aphasic patients seems to rely on neuroplastic strengthening of storage-related mechanisms that seems to be affected by combinatorial linguistic information and retrieving of stored linguistic constructions involves high-frequency oscillatory activity of brain networks, with potential implications also for their combination that needs to be addressed in future research. The storing-and-combining ability seems to be at the biological core of the human language and cognitive and constructionist linguistic approaches need to take this into account. Moreover, this work shows that multidisciplinary approaches that are driven by joint theoretical linguistic and neurobiological hypotheses can be advantageous in the investigation of language in electrophysiological, clinical, and computational experimental settings.

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Appendix [8]

Specification and connectivity of the computational model used in Study 3 – Chapter 4 (The model was developed by Max Garagnani).

Model specification

Each of the 12 simulated areas is implemented as two layers of artificial neuron-like elements ("cells"), 625 excitatory and 625 inhibitory, thus resulting in 15,000 cells in total (see Fig. 5.1.B-C). Each excitatory cell "*e*" consists of an integrate-and-fire neuron with adaptation and simulates a single pyramidal cell, while its twin inhibitory cell "*i*" (see Fig. 1.D) is a graded-response cell simulating the inhibitory response of the cluster of interneurons situated within the same cortical column (Eggert & van Hemmen, 2000; Wilson & Cowan, 1972). The state of each cell x is uniquely defined by its membrane potential $V(x,t)$, specified by the following equation:

$$\tau \cdot \frac{dV(x,t)}{dt} = -V(x,t) + k_1(V_{In}(x,t) + k_2\eta(x,t)) \qquad (1.1)$$

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where $V_{In}(x,t)$ (defined by Eq. (1.2) below) represents the net input to cell x at time t (sum of all inhibitory and excitatory postsynaptic potentials – I/EPSPs), τ is the membrane's time constant, k_1, k_2 are scaling values (see Table S1 for the specific parameter values used in the simulations) and $\eta(\cdot,t)$ is a white noise process with uniform distribution over [-0.5,0.5].

$$V_{In}(x,t) = -k_G \omega_G (A_x, t) + \sum_{\forall y} w_{x,y} \cdot \phi(y,t) \tag{1.2}$$

In Eq. (1.2) above y varies over all cells in the network, $w_{x,y}$ is the weight of the link from y to x, and $\phi(y,t)$ is y's current output (1 or 0), as defined below (Eq. 2); $\omega_G(A_x,t)$ is the area-specific (or "global") inhibition for area A where cell x is located (see explanation below and Eq. 3.3): this term is identical for all excitatory cells x in A and absent for inhibitory cells (k_G is a scaling constant). The weights of inhibitory synapses are assigned a negative sign. Note that noise is an inherent property of each model cell, intended to mimic the spontaneous activity (baseline firing) of real neurons. Therefore, noise was constantly present in all areas, in equal amounts (inhibitory cells have k_2=0, i.e., the noise is generated by the excitatory cells).

The output (or transformation function) ϕ of an excitatory cell e is defined as follows:

$$\phi(e,t) = \begin{cases} 1 & \text{if } V(e,t) - \alpha\,\omega(e,t) > thresh \\ 0 & otherwise \end{cases} \tag{2}$$

Thus, an excitatory cell e spikes (=1) whenever its membrane potential $V(e,t)$ overcomes a fixed threshold *thresh* by the quantity $\alpha\omega.(e,t)$ (where α is a constant and ω, the cell-specific adaptation, is defined below). Inhibitory cells are graded response; the output $\phi(i,t)$ of an inhibitory neuron i is 0 if $V(i,t)<0$ and $V(i,t)$ otherwise.

To simulate spike-rate adaptation (Kandel, Schwartz, & Jessell, 2000, p. 424), function $\omega(\cdot,t)$ is defined so as to track the cell's most recent firing activity. More precisely, the amount of adaptation $\omega(e,t)$ of cell e at time t is defined by:

$$\tau_{ADAPT} \cdot \frac{d\omega(e,t)}{dt} = -\omega(e,t) + \phi(e,t) \qquad (3.1)$$

where τ_{ADAPT} is the "adaptation" time constant. The solution $\omega(e,t)$ of Eq. (3.1) is the low-pass-filtered output ϕ of cell e, which provides an estimate of the cell's most recent firing-rate history. A cell's average firing activity is also used to specify the network's Hebbian plasticity rule (see Eq. (4) below); in this context, the (estimated) instantaneous mean firing rate $\omega_E(e,t)$ of an excitatory neuron e is defined as:

$$\tau_{Favg} \cdot \frac{d\omega_E(e,t)}{dt} = -\omega_E(e,t) + \phi(e,t) \qquad (3.2)$$

In addition to the local excitatory-inhibitory circuits explained in the previous paragraphs (see Fig. 1.D), mediating local competition mechanisms (Duncan, 1996, 2006), the network also implements an area-specific inhibitory mechanism, which serves the main purpose of keeping the total ("global") firing activity of excitatory cells in an area within physiological levels (Braitenberg & Schüz, 1998). This mechanism is assumed to be slower than the excitatory-inhibitory dynamics (which typically leads to oscillations in roughly the gamma range), and is realised by a single graded-response unit that estimates the total firing activity within a model area and then, in turn, inhibits all excitatory neurons proportionally (and by the same amount). The area-specific amount of global inhibition $\omega_G(A,t)$ for area A at time t is defined by Eq. (3.3) below:

$$\tau_{GLOB} \cdot \frac{d\omega_G(A,t)}{dt} = -\omega_G(A,t) + \sum_{e \in A} \phi(e,t) \qquad (3.3)$$

Excitatory links within and between (possibly non-adjacent) model areas are established at random and limited to a local (topographic) neighbourhood; weights are initialised independently and at random, uniformly distributed in the interval]0, 0.1]. The probability of a synapse to be created between any two cells falls off with their distance (Braitenberg & Schüz, 1998) according to a Gaussian function clipped to 0 outside the chosen neighbourhood (a square of size n =19 for excitatory and n=5 for inhibitory cell projections). This produces a sparse, patchy and topographic connectivity, as typically found in the mammalian cortex (Amir, Harel, & Malach, 1993; Braitenberg & Schüz, 1998; Douglas & Martin, 2004; Kaas, 1997).

The Hebbian learning mechanism implemented simulates well-documented synaptic plasticity phenomena of long-term potentiation (LTP) and depression (LTD), as formalised by Artola, Bröcher and Singer (Artola, Bröcher, & Singer, 1990; Artola & Singer, 1993). This rule provides a realistic approximation of known experience-dependent neuronal plasticity and learning (Finnie & Nader, 2012; Malenka & Bear, 2004; Rioult-Pedotti, Friedman, & Donoghue, 2000), and includes both (homo- and hetero-synaptic, or associative) LTP, as well as homo- and hetero-synaptic LTD. In the model, we discretized the continuous range of possible synaptic efficacy changes into two possible levels, $+\Delta$ and $-\Delta$ (with $\Delta \ll 1$ and fixed). Following Artola *et al*., we defined as “active” any (axonal) projection of excitatory cell e such that the estimated firing rate $\omega_E(e,t)$ of cell e at time t (see Eq. (3.2)) is above θ_{pre}, where $\theta_{pre} \in]0,1]$ is an arbitrary threshold representing the minimum level of presynaptic activity required for LTP to occur. Thus, given a pre-synaptic cell i making contact onto a post-synaptic cell j, the change $\Delta w(j,i)$ in efficacy of the (excitatory-to-excitatory) link from i to j is defined as follows:

$$\Delta w(j,i) = \begin{cases} +\Delta & \text{if } \omega_E(i,t) \geq \vartheta_{pre} \text{ and } V(j,t) \geq \vartheta_{+} \quad \text{(LTP)} \\ -\Delta & \text{if } \omega_E(i,t) \geq \vartheta_{pre} \text{ and } \vartheta_{-} \leq V(j,t) < \vartheta_{+} \quad \text{(homosynaptic LTD)} \\ -\Delta & \text{if } \omega_E(i,t) < \vartheta_{pre} \text{ and } V(j,t) \geq \vartheta_{+} \quad \text{(heterosynaptic LTD)} \\ 0 & \text{otherwise} \end{cases} \qquad (4)$$

Furthermore, the implementation of the above rule is subject to the presence, at time-step *t*, of a pre- or postsynaptic spike. In other words, Eq. (4) is applied *only* when the following (inclusive OR) condition holds true:

$\phi(i,t)=1 \vee \phi(j,t)=1$

where $\phi(\cdot,t)$ is defined by Eq. (2). The low-pass dynamics of the cells (Eq. (1.1-2), (3.1-3)) are all integrated using the Euler scheme with step size $\Delta t = 0.5$ ms.

Eq.(1.1)	Time constant (excitatory cells)	τ = 2.5 (simulation time-steps)
	Time constant (inhibitory cells)	τ = 5 (simulation time-steps)
	Total input rescaling factor	$k_1 = 0.01$
	Noise amplitude	
	during learning:	$k_2 = 5\cdot\sqrt{(24/\Delta t)}$
	during testing:	$k_2 = 50\cdot\sqrt{(24/\Delta t)}$
Eq.(1.2)	Global inhibition strength	
	during learning:	$k_G = 0.75$
	during testing:	$k_G = 0.60$
Eq. (2)	Spiking threshold	*thresh* = 0.18
	Adaptation strength	$\alpha = 7.0$
Eq.(3.1)	Adaptation time constant	τ_{ADAPT} = 10 (time steps)
Eq.(3.2)	Rate-estimate time constant	τ_{Favg} = 30 (time steps)
Eq.(3.3)	Global inhibition time constant	τ_{GLOB} = 12 (time steps)
Eq.(4)	Postsynaptic membrane potential thresholds:	
	$\theta_+ = 0.15$	
	$\theta_- = 0.14$	
	Presynaptic output activity required for LTP:	
	$\theta_{pre} = 0.05$	
	Learning rate	$\Delta = 0.0008$

Table 1. Typical parameter values used during the simulations.

Additional evidence in support of the model's connectivity structure

Neuroanatomical evidence shows that adjacent cortical areas tend to be connected with each other through next-neighbour between-area connections (Pandya & Yeterian, 1985; Young et al., 1995; Young et al., 1994). These exist within each triplet of areas of the four domain-specific "sub-systems" modelled, that is, amongst (I) inferior-frontal areas in the articulatory system PF_i – PM_i – M1i, (II) superior-lateral areas in the "auditory" system A1 – AB – PB (Kaas & Hackett, 2000; Pandya, 1995; Rauschecker & Tian, 2000), (III) superior-lateral frontal areas in the "hand-arm" motor system PF_L – PM_L – $M1_L$ (see also Arikuni, Watanabe, & Kubota, 1988; Dum & Strick, 2002, 2005; Lu, Preston, & Strick, 1994), and (IV) inferior temporo-occipital areas in the "visual" system V1 – TO – AT (Distler, Boussaoud, Desimone, & Ungerleider, 1993; Nakamura, Gattass, Desimone, & Ungerleider, 1993).

Evidence also indicates the presence of long-distance cortico-cortical links (see thicker purple arrows in Fig. 3.1B) connecting areas distant from each other. Amongst the long-distance cortico-cortical links within fronto-temporo-occipital cortex, we implemented only the well-documented mutual and reciprocal connections between anterior temporal (AT), superior parabelt (PB), and inferior (PF_i) and superior-lateral (PF_L) prefrontal areas. The connections between inferior anterior (and middle), superior temporal (AT, PB in Fig. 1.B) and inferior prefrontal (and premotor) cortices (PF_i) are realised by the arcuate and uncinate fascicles (Catani, Jones, & Ffytche, 2005; Makris et al., 1999; Makris & Pandya, 2009; Parker et al., 2005; Petrides & Pandya, 2001, 2009; Petrides, Tomaiuolo, Yeterian, & Pandya, 2012; Rilling, 2014; Rilling et al., 2008; Romanski, 2007; Romanski, Tian, et al., 1999). Dorsolateral prefrontal (and premotor) cortex (PF_L) is reciprocally linked to anterior and inferior temporal regions (AT) via the uncinate fascicle (Eacott & Gaffan, 1992; Kuypers, Szwarcbart, Mishkin, & Rosvold, 1965; Pandya & Barnes, 1987, p.49; Ungerleider, Gaffan, & Pelak, 1989; Webster, Bachevalier, & Ungerleider, 1994) as well as to the superior temporal cortex (PB) via the extreme capsule (Pandya & Barnes, 1987, p.48; Romanski, Bates, et al., 1999; Romanski, Tian, et al., 1999; Schmahmann et al., 2007).

Lastly, links between inferior and superior prefrontal areas (PF_i – PF_L) (Yeterian, Pandya, Tomaiuolo, & Petrides, 2012) and between auditory parabelt and anterior temporal cortex (PB

– AT) (Gierhan, 2013) were also implemented, as in a recent (graded-response) version of the architecture (Tomasello et al., 2016).

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Erklärung

Hiermit versichere ich, dass ich die vorgelegene Arbeit selbständig verfasst habe und keine anderen an die angegebenen HIlfsmittel verwendet habe. Die Arbeit ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden

Berlin, Februar 2017

Guglielmo Lucchese