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Bilateral brain reorganization with memantine and constraint-induced aphasia therapy in chronic post-stroke aphasia: An ERP study

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Abstract

Changes in ERP (P100 and N400) and root mean square (RMS) were obtained during a silent reading task in 28 patients with chronic post-stroke aphasia in a randomized, double-blind, placebo-controlled trial of both memantine and constraint-induced aphasia therapy (CIAT). Participants received memantine/placebo alone (weeks 0–16), followed by drug treatment combined with CIAT (weeks 16–18), and then memantine/placebo alone (weeks 18–20). ERP/RMS values (week 16) decreased more in the memantine group than in the placebo group. During CIAT application (weeks 16–18), improvements in aphasia severity and ERP/RMS values were amplified by memantine and changes remained stable thereafter (weeks 18–20). Changes in ERP/RMS occurred in left and right hemispheres and correlated with gains in language performance. No changes in ERP/RMS were found in a healthy group in two separated evaluations. Our results show that aphasia recovery induced by both memantine alone and in combination with CIAT is indexed by bilateral cortical potentials.

Introduction

Language and communication deficits represent major aftermaths of stroke (Berthier and Pulvermüller, 2011, Hillis, 2007). Natural recovery from post-stroke-aphasia (PSA) and functional communication deficits is uncommon and most patients require prolonged rehabilitation to achieve partial improvement (Allen et al., 2012, Salter et al., 2012). In response to the need to develop new treatment strategies for PSA and related deficits, a number of behavioral intervention techniques have been developed based on well-established neuroscience principles (Allen et al., 2012, Salter et al., 2012, Small and Llano, 2009). Intensive and prolonged speech-language therapy (SLT), in which linguistic materials are used in everyday communication and action, is recommended because it is associated with better outcomes than more sparsely applied standard methods (Brady, Kelly, Godwin, & Enderby, 2012). One promising way to speed up recovery and increase the adherence to intensive regimes is to use brief, repetitive action embedded language training. Over more than one decade of research a therapy method known as constraint-induced aphasia therapy (CIAT)[1] (Difrancesco et al., 2012, Pulvermüller et al., 2001) has been determined to be an effective intervention for subacute (Sickert, Anders, Münte, & Sailer, 2014) and chronic PSA (Kurland et al., 2010, Kurland et al., 2012, Pulvermüller et al., 2001). CIAT is a massed-practice regimen performed in a small group of patients or in a dyad (Faroqi-Shah and Virion, 2009, Goral and Kempler, 2009, Kurland et al., 2010, Kurland et al., 2012) that exploits language-action embedding, manipulates task difficulty by using increasingly complex stimuli and responses, and attenuates the deleterious effect of non-use learning which results from the repeated experience of failure to communicate efficiently (Pulvermüller & Berthier, 2008).

In recent years, the original CIAT method realized as a language game simulating request communications has been successfully applied not only to patients with mild-to-moderate severe aphasia but also to moderate-to-severe cases coexisting with apraxia of speech (Kurland et al., 2012). CIAT has also been expanded and restructured to uncover expressive language exercises, verb training in narrative generation, reading, and writing with home practice in everyday communication (Goral and Kempler, 2009, Johnson et al., 2014, Meinzer et al., 2005, Szaflarski et al., 2008). Nevertheless, the role of augmenting gains provided by CIAT with a cognitive enhancing drug has been evaluated only in one study so far (Berthier et al., 2009). The drug used in that trial was memantine, a moderate affinity, uncompetitive *N*-methyl-D-aspartate receptors (NMDArs) antagonist with strong voltage-dependency and fast kinetics that blocks the excessive activity of glutamate without interfering with physiological glutamatergic neurotransmission (Parsons, Stöffler, & Danysz, 2007). Animal models of ischemic stroke showed an upregulation of NMDArs in ischemic cores and surrounding cortical regions (Qü et al., 1998, Shih et al., 2013) and also that treatment with memantine reduced the size of the infarcts and alleviated cognitive deficits (Shih et al., 2013) Moreover, chronic oral treatment with memantine (28 days) in mice with experimentally-induced infarcts improved stroke outcomes by promoting sensory map recovery, decreased reactive astrocytosis, increased vascular density, and increased brain-derived neurotrophic factor (BDNF) and tropomyosin-related-kinase-B receptor expression (López-Valdés et al., 2014). Experimental studies showed three key findings which may provide some clues for understanding the role of memantine in chronic PSA: first, abnormal glutamate activity extends beyond the acute period (Hota et al., 2008, Jagadapillai et al., 2014); second, stroke outcome can be improved with memantine in acute and chronic phases; and third, memantine may promote other mechanisms of brain reparation, besides stabilizing glutamate activity to more physiological levels (López-Valdés et al., 2014). In humans, prolonged treatment with memantine has been found to be effective in chronic cognitive deficits associated with vascular dementia (Levine and Langa, 2011, Orgogozo et al., 2002, Wilcock et al., 2002) as well as on language and communication deficits among patients with Alzheimer's disease and Parkinson's disease complicated with dementia (*for review see* Tocco et al., 2014). Future studies using neuroimaging methods (e.g., proton MRI spectroscopy) measuring metabolites (glutamate/glutamine) implicated in the neuronal-glial neurotransmission system may inform on the relationship between post-stroke language and communication deficits and glutamate activity in language-eloquent regions, and their potential modulation with memantine (see Cirstea et al., 2011).

The drug trial modulating glutamatergic activity in chronic PSA was a randomized, double-blind, placebo-controlled study that examined the role of memantine alone and combined with CIAT in improving aphasia severity (Berthier et al., 2009). Treatment with memantine alone (not associated to aphasia therapy) improved aphasia severity significantly more than placebo alone. The addition of CIAT (two weeks) provided highly significant benefits in both groups, but gains were more marked with memantine and these differences were maintained during the follow-up evaluation two weeks later. The present study examines the functional brain correlates of language processing using ERP induced by memantine/placebo alone and by these agents combined with CIAT in the same sample of patients (Berthier et al., 2009). ERP methods were preferred over alternative brain activation measures such as functional magnetic resonance imaging (*f*MRI) because their ease of application in patients and because a range of pre-existing results indicate that brain correlates of language recovery are manifest in the electrocortical response (Berthier et al., 2011).

In recent years, functional neuroimaging studies have highlighted the brain areas that mediate spontaneous and treatment-induced recovery from PSA through neural plasticity. Neural plasticity is more efficient when it depends on behavioral experience (e.g., motor training; aphasia therapy) (Cramer et al., 2011, Dobkin and Dorsch, 2013, Kleim and Jones, 2008, Nudo, 2013). Restorative neural plasticity promoted by successful CIAT in PSA has been examined with *f*MRI (Kurland et al., 2012, Meinzer and Breitenstein, 2008, Richter et al., 2008) and other methods (see below). Five *f*MRI studies have been performed and although their results were fairly inconsistent probably because training-induced network remapping was different

depending on lesion sites and volumes, all studies reported marked functional neuroplastic changes in both perilesional and right hemisphere regions (Kurland et al., 2010, Kurland et al., 2012, Meinzer and Breitenstein, 2008, Mohr et al., 2014, Richter et al., 2008). In addition, changes in the time course and localization of different language processes in perilesional and right hemisphere areas have been correlated with recovery from aphasia using magnetoencephalography (MEG) (Breier et al., 2009) and event-related potentials (ERP) (Pulvermüller, Hauk, Zohsel, Neininger, & Mohr, 2005). These latter methods are especially telling as they monitor brain activation with millisecond precision and therefore provide the fine grained temporal resolution to follow fast language comprehension processes on-line (Friederici, 2011, Pulvermüller et al., 2009).

Section snippets

Patients

Patients were recruited through advertisements in local language rehabilitation centers, aphasia support groups and newspapers. Inclusion criteria were: age between 18 and 70 years, unilateral left hemisphere infarctions or hemorrhages, diagnosis of aphasia based on scores on the Western Aphasia Battery-Aphasia Quotient (WAB-AQ)<93.8 (Kertesz, Pascual-Leone-Pascual, & Pascual-Leone-García, 1990), and aphasia duration⩾1 year. Exclusion criteria were: incapacity to receive CIAT and…

Patient characteristics

A total of 28 patients were included and 27 of them completed the trial. The CONSORT diagram showing the flow of participants is shown in Fig. 1. Baseline characteristics of memantine and placebo groups are shown in Table 1. The aphasia profiles of the groups were relatively similar and representative of typical samples of patients with chronic PSA. Groups were well matched with respect to baseline demographic and clinical characteristics, except for time since stroke onset which tended to be…

Discussion

In this study, we used ERP elicited by written words to monitor any neurophysiological changes of language-related brain activity brought about by application of the NMDArs inhibitor memantine and CIAT in patients with chronic PSA. Our major findings were the following. First, during the initial evaluation, just before the PSA patients received the drug or placebo, ERP in both groups showed significant activity increases in brain activity (P100 and N400) in comparison to the group of healthy…

Conclusions

In summary, memantine alone decreased signal activity on ERP and these changes were correlated with improvement in aphasia. This raises the possibility that memantine may readjust neuronal activity to a more physiological level in stroke patients promoting recovery from aphasia. Our neurophysiological data further suggest that memantine unpaired with aphasia therapy strengthened compensatory rewiring in both cerebral hemispheres and prepares the brain for better responses to brief, intensive…

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...Treatment gains can be augmented and speeded up with cognitive enhancing drugs and non-invasive brain stimulation (Basilakos et al., 2022; Berthier et al., 2009; Berthier, 2021). For instance, a randomized controlled trial (RCT) in chronic PSA showed that the glutamatergic modulator Memantine alone and in combination with ILAT produced significant language and communication benefits, which resulted in an increase of neural activity in both hemispheres (Barbancho et al., 2015; Berthier et al., 2009). Furthermore, an open-label case-controlled study and a cross-over RCT also showed that two weeks of ILAT produce significant improvements in depressive symptoms in PWA (Berthier et al., 2022; Mohr et al., 2017)....

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...Thematic domain #3: Understanding unimpaired language processing (23 studies identified) – Studies that used aphasia as a model to inform our knowledge about how the unimpaired language system operates (e.g., comparing ERP responses reflecting phonological-phonetic encoding between PWA and healthy controls to draw conclusions about the time-course of unimpaired encoding; Laganaro, Python, & Toepel, 2013). Thematic domain #4: Tracking response to therapy (15 studies identified) – Studies that used ERP methods to identify changes in neural function in response to some form of intervention (e.g., measuring changes in P100 and N400 responses following treatment with memantine and with constraint-induced language therapy; Barbancho et al., 2015). Thematic domain #5: Assessing language and/or cognition (14 studies identified) – Studies that focused on the potential for using ERPs as a proxy for behavioral language and/or cognitive assessment (e.g., using ERPs to predict auditory comprehension skills; Kojima & Kaga, 2003)....

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