The Effects of the Glutamate Antagonist Memantine on Brain Activation to an Auditory Perception Task

Heidi van Wagneningen,^{1*} Hugo A. Jørgensen,^{2,3} Karsten Specht,^{1,4}
Tom Eichele,¹ and Kenneth Hugdahl^{1,2}

¹Department of Biological and Medical Psychology, University of Bergen, Norway

²Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

³Department of Clinical Medicine, Psychiatry, University of Bergen, Norway

⁴Clinical Engineering Department, Haukeland University Hospital, Bergen, Norway

Abstract: Glutamate is critically involved in the regulation of cognitive functions in humans. There is, however, sparse evidence regarding how blocking glutamate action at the receptor site during a cognitive task affects brain activation. In the current study, the effects of the glutamate antagonist memantine were examined with functional magnetic resonance imaging (fMRI). Thirty-one healthy adults were scanned twice in a counter-balanced design, either in a no-drug session or after administration of memantine for 21 days. The subjects performed a simple auditory perception task with consonant-vowel stimuli. Group-level spatial independent component analysis (ICA) was used to decompose the data and to extract task-related activations. The focus was on four task-related ICA components with frontotemporal localization. The results showed that glutamate-blockage resulted in a significant enhancement in one component, with no significant effect in the other three components. The enhanced effect of memantine was in the middle temporal gyrus, superior frontal gyrus, and middle frontal gyrus. It is suggested that the results reflect effects of glutamatergic processes primarily through non-*N*-methyl-*D*-aspartate (NMDA) receptor pathways. Moreover, the results demonstrate that memantine can be used as a probe which allows for studying the effect of excitatory neurotransmission on neuronal activation. *Hum Brain Mapp* 30:3616–3624, 2009. © 2009 Wiley-Liss, Inc.

Key words: memantine; glutamate; NMDA receptor; cognitive functions; fMRI; ICA

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*Correspondence to: Heidi van Wagneningen, Department of Biological and Medical Psychology, University of Bergen, Jonas Lies Vei 91, 5011 Bergen, Norway. E-mail: heidi.wagneningen@psybpuib.no

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INTRODUCTION

The amino acid glutamate is the primary excitatory neurotransmitter in the brain and plays a critical role in fast excitatory synaptic transmission [Cooper, 2002]. The ionotropic *N*-methyl-*D*-aspartate (NMDA) receptor is the most frequent and widely distributed receptor throughout the brain. The receptor has a high affinity for glutamate and it is involved in excitatory synaptic transmission, plasticity, and excitotoxicity in the central nervous system [Cull-Candy et al., 2001]. Glutamatergic neurotransmission is essential for healthy neurocognitive function, and malfunction at the NMDA receptor site has been implicated in several neurological and psychiatric disorders, such as

Alzheimer's disease and schizophrenia [Beal, 1995; Olney et al., 1999]. Human studies of NMDA receptor function have been limited by the lack of suitable, well-tolerated pharmacological probes [Herrling, 1992; Krystal et al., 1994]. Memantine, however, is a low affinity voltage-dependent uncompetitive antagonist of the NMDA receptor, binding to the modulatory Mg^{2+} site in the ion-channel [Robinson and Keating, 2006; Rogawski and Wenk, 2003]. The moderate affinity, high voltage-dependency and fast blocking-unblocking kinetic allow memantine to rapidly leave the NMDA channel during physiological activation but block the receptors under peak activity (e.g., pathological conditions) [Danysz et al., 2000]. Because of the effect and tolerability, memantine is now an approved treatment for moderate to severe Alzheimer's disease. For the same reasons, memantine is an interesting candidate for testing the relationship between glutamatergic neurotransmission and cognitive function in healthy individuals, particularly effects on brain activation. The results from the few studies that have focused on the neuronal effects of memantine [Korostenskaja et al., 2007; Rammsayer, 2001; Schugens et al., 1997; Schulz et al., 1996] suggest that a single dose could affect cognition in healthy individuals.

Blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI), with its superior spatial resolution, can be used to explore mechanisms of drug action in the central nervous system in a system-wide and noninvasive way. The aim of the current study was therefore to use fMRI for evaluating the effect of memantine on brain activation and cognitive function in healthy individuals.

A group-level spatial independent component analysis (ICA) [Calhoun et al., 2001] was used to decompose the BOLD data into maps and time courses that were separately tested for effects of memantine administration. ICA was employed for three reasons: (1) Any drug manipulation might affect neurovascular transfer, and ICA affords a data-driven analysis of fMRI data without making assumptions about the parameters of the hemodynamic response to stimulation; (2) ICA extracts components that are task/function-related but produce time courses that are not strongly correlated with the timing of the stimulation; (3) the contribution of task-unrelated background activity and localized physiological noise to each measurement is captured in separate components [Calhoun and Adali, 2006]. As memantine might affect the hemodynamic transfer function, as well as these different types of signals, ICA was deemed more appropriate than modeling the data in the general linear model. The functional relevance of the different ICA components was assessed by analyzing the relationship between stimulation and the component amplitudes. It was expected that the ICA analysis would reveal separate components which on one hand correlate with the stimulation but on the other hand separate functionally different networks, like auditory perception from cognitive processing [Specht et al., 2008]. To our knowledge, there are no fMRI studies inves-

tigating the effects of memantine on brain function in relation to a perceptual task. There are, however, a few studies using ketamine as blocking agent. Abel et al. [2003a,b] found both increase and decrease in task-related activation when blocking NMDA receptor function. Thus, it is an open question whether task-related effects on the BOLD signal of memantine will result in enhancement or reduction of activation in specific brain areas.

METHODS

Participants

Forty participants were initially screened, and six were excluded. Exclusion criteria were psychiatric or neurologic diagnosis, current pregnancy or breastfeeding, other ongoing medication (except for oral contraceptives), epilepsy, cardiovascular diseases, special diet, and allergies. Female participants were required to have a negative urine pregnancy test at baseline, and to use an effective method of birth control before entry and throughout the study. All participants were pretested with the dichotic listening task before inclusion and only those with a right ear advantage (i.e., more correct reports from the right ear stimulus in the no attention instruction condition, see auditory perception task) were included. Furthermore, the participants were screened with audiometric testing to ensure normal hearing on both ears for the frequencies of 500, 1,000, 2,000, and 4,000 Hz. Participants with a threshold higher than 20 dB on any frequency or an interaural difference larger than 15 dB were excluded from the study. Of the remaining 34 participants, one participant withdrew from the study because of experienced discomfort, two other participants were excluded because of excessive artifacts during the MRI scanning. No serious adverse events occurred during the study or during the initial 30 days following the study, as determined by personal contact with the physician (H.A.J.) being responsible for the drug administration and continuous follow-up.

The data reported here are from 31 right-handed healthy adults (17 males, 14 females; mean age 23.9 years ($SD = 3.61$), mean body weight 72.17 ($SD = 11.01$, $n = 29$). Handedness was determined from a 15-item handedness questionnaire [Raczkowski et al., 1974] and to be included in the study 13 of the 15 items had to be checked for right hand (or right foot, one item) use. Participants were instructed to avoid nicotine and caffeine for at least 2 h before the MR scanning.

All participants received written and oral information about the project, the procedure at the laboratory, and about memantine, before inclusion in the study. All participants gave written informed consent and were paid a compensation for their expenses and use of time. The study protocol (EUDRACTNR. 2005-002640-26) was approved by the Norwegian Medicines Agency, The Norwegian Social Science Data Service, and the Regional Committee for Medical Research (REK) and was carried out

according to the declaration of Helsinki. Participants were insured by the Drug Liability Association (which is obligatory for all pharmacology studies in Norway in accordance with Chapter 3 in The Norwegian product liability act of 23.12.88 nr.104.).

Pharmacological Intervention

Memantine (Ebixia®), H. Lundbeck A/S (EU/1/02/219/002/NO), was used for the pharmacological intervention. Memantine is generally well-tolerated [Areosa et al., 2005], and the most frequently occurring adverse events ($\leq 1\%$ of elderly patients) include the following: confusion, dizziness, drowsiness, headache, insomnia, agitation, and/or hallucinations. Less common adverse effects include the following: vomiting, anxiety, hypertonia, cystitis, and increased libido. None of the participants reported any severe side effects. One participant was excluded after 1 week of memantine 10 mg per day due to intolerable dizziness and nausea. Among the remaining, 50% reported slight tiredness and dizziness in the first day of treatment and at few instances this was also reported at the highest dose (20 mg). In two participants, dizziness was combined with slight nausea.

Drug Administration Procedure

Memantine was administered orally as tablets to be taken every day for 21 days. To ensure compliance, the blister packings were controlled three times during the drug administration. To reduce the risk of side effects, the dose of memantine was increased weekly from 10 to 15 to 20 mg per day to obtain close to steady-state plasma level after 21 days. The participants were scanned twice in a counter-balanced way, in a no-drug session and after 21 days on memantine. The participants who were scanned first time when on memantine had the second MR-scanning at least 30 days after the initial scanning to make sure that the drug was eliminated from the body.

Auditory Perception Task

An auditory speech perception task was used with dichotic presentations of consonant-vowel (CV) syllables [Hugdahl, 2003]. Dichotic presentation means that two different syllables were presented on each trial. To control for biasing attention to either the right or left ear stimulus, the participants were instructed to focus attention on the right ear stimulus in 1/3 of the trials, on the left ear stimulus in 1/3 of the trials, and with no attention focus instruction in 1/3 of the trials. In the no attention condition, they were instructed to report the CV-syllable they heard first or best. The data are presented as the average across the three attention instruction conditions. The syllables were read by an adult voice and they were digitally recorded,

stored, and presented through MR-compatible headphones (NordicNeuroLab Inc., Bergen, Norway, www.nordicneurolab.no) using E-prime software (www.psnet.com). The headphones also served to attenuate background noise (-40 dB) from the MR magnet gradients. Written instructions about the procedure were shown via LCD goggles (NordicNeuroLab, www.nordicneurolab.no). The participants responded verbally on each trial through an in-house built air-conducting microphone, placed on the head-coil, and connected to a digital recorder (M-Audio Microtracker 24/96, www.m-audio.com) outside the MR chamber, which recorded the verbal responses from each participant, for later scoring.

MR Imaging

MR imaging was performed with a 3.0 T GE Signa HDx scanner, using a single-channel head coil. Head movements were restrained by additional padding inside the head coil. For positioning the slices for functional imaging parallel to the AC-PC line, a high-resolution T1-weighted 3D volume image was acquired before the echo planar imaging (EPI) image acquisitions using a FSPGR pulse sequence with 122 sagittal slices (64×64 , 1.0 mm thickness, TE 30 ms, repetition time (TR) 1,500 ms, flip angle (FA) = 90). The fMRI part involved a sparse-sampling EPI acquisition scheme [Hall et al., 1999] in which the EPI volumes were acquired with TR = 5.5 s and acquisition time (TA) = 1.5 s, with silent gap of 4 s, during which the stimuli were presented and the oral responses were recorded, following the procedure recently suggested by van den Noort [2008]. A block design with nine ON-OFF block combinations was used. In total, 184 BOLD sensitive EPI volumes were acquired with $3.44 \times 3.44 \times 5.5$ mm³ voxels and 25 axial slices covering most of the cerebrum. The first four EPI volumes were rejected before the processing of the data.

fMRI Data Analysis

The DICOM images were converted to analyze format using commercially available software (nICE, <http://www.nordicimaginglab.no>). Preprocessing was performed within the statistical parametric mapping software SPM5 (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk) implemented in Matlab R2006a (Mathworks Sherborn, MA, www.mathworks.com). First, the images were realigned and corrected for possible movement correlated images distortions (unwarp). Then, the realigned images were normalized into the Montreal Neurologic Institute (MNI) reference brain space [Ashburner and Friston, 1999], using a normalized EPI template, included in the SPM5 software. The normalized images were then resampled with a voxel size of $3 \times 3 \times 3$ mm³ and smoothed with a Gaussian kernel filter of 8 mm full-width at half maximum. Thereafter, a group-level spatial ICA [Calhoun et al., 2001] was performed using the GIFT

toolbox, version 1.3c (<http://icatb.sourceforge.net>). As group ICA requires that all participants are analyzed at once, a method for data reduction using principal component analysis (PCA) allows all datasets to be loaded at one time [Calhoun et al., 2001]. In the PCA step, data from each participant were reduced from the number of time points within the study ($n = 180$) to 25 dimensions and concatenated to a single dataset. A group spatial ICA then decomposed the data into 25 components, using the infomax algorithm [Bell and Sejnowski, 1995], with subsequent back-reconstruction into single participants. The resulting output was a map and an associated time course for every component and participant. As a measure of activation, the ON-OFF block difference, expressed in mean percent signal change in the component time courses averaged over block repetitions, was used. The ON condition refers to blocks when the task was performed, and the OFF condition represents a low-level (resting) baseline. Task-related components with the largest effects, e.g., positive signal change with frontotemporal localization, were selected for further processing. Correlation between independent components (IC) with the task was tested by convolving the box-car function representing the stimulus timing with a canonical hemodynamic response and entered into a multiple linear regression analysis, predicting the observed IC time course. The percentage variance accounted for (PVAf, R^2) were averaged across subjects and individual scaling parameters (β) were entered into one-sample t -tests against zero magnitude. Components with robust t -statistics ($P < 0.001$) and at least moderate correlation with the stimulus timing were selected for further processing.

This resulted in four components that were chosen because they showed the largest ON-OFF differences and (near) significant differences due to the memantine manipulation. A number of other ICs did show time courses with weaker positive/negative block response that followed the paradigm timing, but did not show differences between the two sessions (memantine, no-drug) and were not taken into further consideration. Other component maps and their time courses were suggestive of typical fMRI signals of no interest, i.e., motion, cerebro spinal fluid (CSF), large vessels, susceptibility, and were not considered further.

The four task-related ICs were followed up by testing the temporal and spatial characteristics of these components. First, the effect of memantine on the activation strength was tested by comparing the ON-OFF difference across sessions (memantine versus no-drug) with paired t -tests and was considered significant at $P < 0.01$. Second, the spatial distribution of these selected components were tested by subjecting the component maps for each session to a second level random effect spatial test in SPM5, i.e., the IC weights at every voxel were entered into a one-sample t -test against zero magnitude. Similarly, spatial differences across sessions (memantine versus no-drug) were tested with a paired t -test. Effects were considered signifi-

cant at a false discovery rate (FDR) corrected threshold of $P < 0.01$ with a cluster extent of 10 voxels.

RESULTS

Behavioral Data

A repeated measures analysis of variance based on the design Group (no-drug, memantine) $\times$ Ear (right, left) replicated previous findings with overall better recall of the right ear stimulus, $F(1,30) = 21.414$, $P = 0.00007$. There were no significant session effects between the no-drug and memantine conditions, or order of effects.

fMRI Data

IC time courses

From the group ICA, four of the 25 ICs displayed large (mean percent signal change) ON-OFF block differences with frontotemporal localization (Fig. 1). Figure 1 also shows that memantine did not seem to modulate the shape of the BOLD response for the four selected ICs. The effect of memantine was evaluated as the change of the ON-OFF difference across sessions with paired t -tests. Furthermore, the paradigm regressors were correlated with the time courses of the components. The result of the correlation between the component time courses and paradigm regressors for IC1 after memantine administration showed that the average percentage of variance accounted for by the model was 36.79% ($SD = \pm 15.97$), the random effects statistic over the individual scaling factors yielded a significant effect ($t = 6.23$, $P < 0.001$), and for IC1 no-drug (39.21%, ± 20.24 , $t = 6.04$, $P < 0.001$). IC1 showed the largest ON-OFF difference and also showed significantly larger activation in the memantine session compared with the no-drug session (mean percent signal change difference between sessions: 0.38%, $SD = 0.79$, $t = 2.55$, $df = 30$, $P = 0.01$). For IC2 after memantine administration, the average percentage of variance accounted for by the model was (22.13%, ± 13.28 , $t = 6.24$, $P < 0.001$) and for IC2 no-drug (19.45%, ± 17.15 , $t = 5.79$, $P < 0.001$). For IC3 after memantine administration, the average percentage of variance accounted for by the model (47.25%, ± 16.63 , $t = 7.74$, $P < 0.001$) and for IC3 no-drug (41.87%, ± 18.60 , $t = 7.19$, $P < 0.001$). IC2 and IC3 showed a similar tendency as IC1 on the average; however, the effect of the ON-OFF block differences across sessions (memantine vs. no-drug) was not significant. For IC4 after memantine administration, the average percentage of variance accounted for by the model (22.85%, ± 11.37 , $t = 6.52$, $P < 0.001$) and for IC4 no-drug (20.19%, ± 13.33 , $t = 10.14$, $P < 0.001$). IC4 showed no significant ON-OFF block differences across sessions (memantine vs. no-drug).

The comparison of the average percentage of variance accounted for by the model between memantine and no-drug sessions resulted in a significant effect in IC1 ($t =$

Figure 1.

The figure displays the BOLD amplitude ON–OFF block difference, expressed as percentage positive signal change in IC1–4 for the memantine and no-drug sessions. In the memantine session, the components 1–4 are displayed in different colors (red = IC1, blue = IC2, green = IC3, and purple = IC4), whereas the no-drug session are displayed in grey color for IC1–4.

2.52, $P < 0.05$), whereas IC2 ($t = 1.70$, $P < 0.10$), IC3 ($t = 1.41$, $P < 0.17$), and IC4 ($t = 0.21$, $P < 0.83$) did not show significant differences.

IC maps

Significant activations based on one-sample t -tests for each component and session (FDR corrected, $P < 0.01$, with a cluster extent of 10 voxels), are shown in Figure 2. Spatial differences across sessions (memantine, no-drug) were tested for each of the four ICs (paired t -tests, uncorrected, $P < 0.001$, with a cluster extent of 10 voxels); however, there were no significant session effects in the spatial organization of the ICs.

The corresponding anatomical localizations and other statistical parameters for each of the four ICs are given in Supporting Information Tables I–IV.

IC1 showed significant activation foci bilateral in the middle temporal gyrus and in the superior frontal gyrus, and middle frontal gyrus, in the left superior temporal gyrus, inferior temporal gyrus, precentral gyrus and precuneus (Supporting Information Table I) The temporal

lobe pattern of activation correspond to areas activated to acoustic stimuli [Seifritz et al., 2002]. These components also showed a pattern of activation that can be associated with speech processing [Binder et al., 2000; Hugdahl et al., 1999; Jancke and Shah, 2002; Rimol et al., 2005; Specht and Reul, 2003]. Moreover, the frontal activation showed a pattern of activation associated with attention and cognitive control functions [Hugdahl et al., 2008]. IC2 showed significant activation foci bilaterally in the superior temporal gyrus, in the left cingulate gyrus, superior and medial frontal gyrus, insula, postcentral gyrus, and bilaterally in the inferior parietal lobule (Supporting Information Table II). The predominantly frontopolar areas reflected in the spatial map from IC2 (Supporting Information Table II) have been described in earlier studies and have been proposed to be involved in executive control and working memory functions [Esposito et al., 2006; Miller and Cohen, 2001]. The temporal lobe activation pattern seen in IC2 (Supporting Information Table II) show a similar pattern of activation that correspond to response of auditory stimuli described by [Hugdahl et al., 2000] and natural audiovisual stimuli [Malinen et al., 2007]. IC3

Figure 2.

The figure displays the spatial extension of ICI-4 (red = IC1, blue = IC2, green = IC3, purple = IC4, slice position 0 mm in MNI space) for the no-drug and memantine sessions (FDR corrected at $P < 0.01$, with a cluster extension of 10 voxels).

showed activation foci in the superior and medial temporal gyri, the superior and medial frontal gyri, cuneus and precuneus (Supporting Information Table III). Clusters in IC3 showed significant areas of activation that are known to be related to speech perception [Hugdahl et al., 1999]. There were also additional activation in postcentral/precentral gyrus associated with speech production [Specht and Reul, 2003; van den Noort et al., 2008]. IC4 showed activation foci bilaterally in the superior temporal gyri and the transverse temporal gyrus, in the middle temporal gyrus, claustrum, insula, thalamus, and precentral gyrus (Supporting Information Table IV), and for the memantine condition there was additional activation in insula, precentral gyrus, and thalamus (Supporting Information Table IV). The pattern of activation seen in IC4 is similar to what is seen in low-level auditory target processing [Eichele et al., 2005; Kiehl et al., 2005].

DISCUSSION

The present study demonstrated that modulation of the glutamatergic system using the NMDA receptor antagonist memantine was associated with selectively enhanced

amplitude of the BOLD signal change in one task-related component (IC1), whereas other task-related components were marginally affected by memantine.

It can be suggested that the current results primarily reflect the effect of a non-NMDA receptor based glutamatergic enhancement [Moghaddam et al., 1997]. Deakin et al. [2008] have suggested that some of the effects of NMDA antagonist may be mediated by enhanced glutamate release onto non-NMDA receptors, whereas others may be directly mediated by reduced NMDA function. Thus, the current results rather reflect effects of enhanced glutamatergic processes through non-NMDA receptors. Korostenskaja et al. [2007] suggested that the amplitude increase of the mismatch negativity event related potential after memantine administration may be mediated through indirect effects of aminergic modulation on NMDA receptors. Previous biochemical studies have indicated that NMDA receptors antagonists may enhance the release of endogenous glutamate and aspartate [Bustos et al., 1992; Liu and Moghaddam, 1995]; moreover, this enhancement may further activate glutamatergic neurotransmission at non-NMDA receptors. Memantine may have effects on non-NMDA receptors, such as 5HT3 receptor [Rammes

et al., 2001], or at different nicotinic nACh receptors at potencies possibly similar to the NMDA receptor [Aracava et al., 2005; Buisson and Bertrand, 1998; Chen and Lipton, 2006]. Thus, synergistic properties of memantine on these receptors could contribute to the enhanced amplitude of BOLD signal change seen in IC1 after memantine administration. The current study does not allow disentangling if the enhancement of the amplitude of BOLD signal change might be due to altered connectivity between regions or if it may be due to effects of enhancement of glutamatergic processes through non-NMDA receptors.

The activated patterns found for IC1 correspond to areas typically activated to tasks involved in auditory and speech processing [Specht and Reul, 2003], and in attention and cognitive control functions [Hugdahl et al., 2009]. There seems to be consensus in the literature that cognitive control is related to the function of the frontal lobes [Stuss et al., 2002] and the dorsal part of the anterior cingulate cortex [Bush et al., 2000]. The prefrontal cortex is proposed to be important when top-down processing is needed. Schizophrenia patients have repeatedly shown impaired functions in tasks requiring top-down cognitive control and response suppression [Green, 1998; Heinrichs, 2000; Rund et al., 2006], this might be due to altered glutamatergic neurotransmission in these patients. Moreover, this assumption is further supported by findings from magnetic resonance spectroscopy studies showing lower levels of glutamatergic metabolites in these patients compared with healthy controls, in areas known to be involved in tasks requiring top-down cognitive control and response suppression [Theberge et al., 2003; Tsai et al., 1995]. The enhanced amplitude of BOLD signal change in auditory areas related to speech processing [Specht and Reul, 2003] in IC1 are in line with the task-related changes in BOLD signal demonstrated by Abel et al. [2003b] for an visual task after ketamine administration.

IC (1–3) are overlapping, in particular, in the medial frontal cortex. This means that the time courses found for IC (1–3) are linearly combined in regions of overlap. The peaks of the maps are sparse, and overall the maps are spatially independent, but regionally overlaps can and will occur in ICA. Thus, in addition to the regional overlap in the medial frontal wall, including the supplementary motor area, ACC, and superior frontal gyrus, the temporal overlap might pertain to the overall integrative role of the medial frontal cortex for higher cognitive processes reflecting the instruction-induced attention focus to either side of the auditory space.

Behavioral performance did not differ between the two sessions; thus, differences in the BOLD amplitude cannot be explained as the result of performance differences between the no-drug and memantine sessions. Results from several fMRI studies investigating the effects of the NMDA antagonist ketamine on brain activation in relation to a cognitive task have typically not affected the behavioral performance, but still showed changes in brain networks that subserve the cognitive process that has been

studied [Abel et al., 2003a; Corlett et al., 2006; Fu et al., 2005; Honey et al., 2004; Northoff et al., 2005]. Thus, pharmacological imaging could have an important indirect clinical consequence as alterations in neuronal responses could occur before a behavioral deviation. Although the former is already detectable with fMRI, the latter might occur in a more severe degradation.

There are limitations to this study, the participants repeated the same task on three occasions; however, this was controlled for by using a counter-balanced design and there was no significant effects of sequence across sessions. Furthermore, plasma level concentrations were not measured; however, instead of administering a single dose memantine was stepwise increased from 10 mg per day to 20 mg per day and administered for 21 days to obtain steady-state plasma levels concentrations. It is reported from clinical trials that a daily dose of 20 mg lead to steady-state plasma concentrations of memantine estimated to remain in the order of 0.5–1 μmol [Parsons et al., 1999]. Moreover, compliance was controlled for by control of empty blister packings three times during the drug administration. Moreover, pharmacological imaging studies are often confounded by an interaction between the effects of the drug and the effects of vascular parameters, the so-called neurovascular confound. Thus, the possibility that memantine altered the BOLD signal because of an impact on global cerebral blood flow (CBF) via systemic cardiovascular effects cannot be excluded. Whether or not memantine does produce an effect on neurovascular coupling could not be tested directly in the current experimental set-up. However, based on previous studies examining the effects of memantine administration in healthy volunteers [Hergovich et al., 2001; Study MRZ90001-2040, 1985], it is not expected that memantine has vasoactive properties that alters the BOLD signal because of an impact on global CBF via systemic cardiovascular effects, and not in response to the cognitive task performed. Our results are confirming this by showing a drug effect only in one component (IC1) whereas the BOLD signal from the other ICs were not significantly different between the memantine and no-drug sessions. Thus, these findings support that memantine does not directly affect global or local CBF independent of the cognitive task performed.

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