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Are cholinergic enhancers beneficial for memory in schizophrenia? An event-related potentials (ERPs) study of rivastigmine add-on therapy in a crossover trial

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Abstract

Studies have reported beneficial effects of cholinergic enhancers, e.g., rivastigmine, on memory in schizophrenia but others have not. Possibly, these discrepancies are related to the lack of specificity of the tests used. This study investigated the effect of rivastigmine on memory in schizophrenia using event-related potentials (ERPs). Eighteen patients treated with atypical antipsychotic received rivastigmine adjuvant therapy in a randomized, crossover design. They were assessed at baseline (T1) and on two subsequent occasions (T2 and T3), where one half of the subjects were taken rivastigmine and the other half not. ERPs were recorded during a recognition memory task on each session. Behavioral and ERP data were analyzed using mixed ANOVA models first at T1 to detect potential group differences and for the trial (T1–T2) to determine the influence of rivastigmine, i.e., session×group interactions. The results showed no group difference at T1 except a trend for one group to be less efficient than the other on RT measures. When controlling for this difference the results on the trial data showed a trend for a benefit of rivastigmine on the RT memory effect. ERP analysis revealed that rivastigmine affects the amplitudes of two components elicited within 150–300 ms over posterior (reduced N2b) and frontal sites (enhanced P2a). It also enhances the magnitude of the memory (old/new) effect on two later components over posterior (N400) and frontal sites (F-N400). These results suggest that rivastigmine improves selective attention by enhancing interference inhibition processes (P2a) and lowering the reactivity to incoming stimulus (N2b). It also improves the integration of information with knowledge (N400) and with its context (F-N400). Generally, this study showed that the beneficial effect of rivastigmine on memory is not unitary but rather comes from its action at different time points within information processing cascade.

Keywords: Cognitive enhancers; Event-related potentials; Memory; Rivastigmine; Schizophrenia

1. Introduction

Cognitive impairments in schizophrenia, particularly those affecting memory, have long been reported as a major factor interfering with prognosis and social reintegration (Green, 1996; Harvey et al., 1997). Despite the favorable effects of many atypical antipsychotics, cognitively challenged patients with schizophrenia remain impaired with regards to normative data.

A relationship between acetylcholine (ACh) and cognition, especially memory, has been relatively well established in healthy subjects (Mesulam, 1990, 1995) and it is widely acknowledged that central ACh dysfunction play a major role in the cognitive impairments found in dementia of Alzheimer's type (Lawrence and Sahakian, 1998; Cummings, 2000; Mega, 2000). Numerous studies have also reported anomalies in the central ACh system in schizophrenia such as reduced numbers of nicotinic and muscarinic receptors (Breese et al., 2000; Crook et al., 2001; Freedman et al., 2000; George et al., 2000) or in ACh subcortical interneurons (German et al., 1999; Holt et al., 1999). These observations support the earlier suggestion that

Abbreviations: Ach, acetylcholine; AChE, acetylcholinesterase; DA, dopamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalogram; EOG, electroocculogram; ERPs, event-related potentials; FTND, Fagerström Test for Nicotine Dependence; ISI, inter-stimulus interval; LTP, long-term potentiation; PANSS, Positive and Negative Symptoms Scale; PCP, phencyclidine; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; THC, tetrahydrocannabinol.

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the ACh system may play a key role in the pathophysiology of schizophrenia through the cholinergic–dopaminergic balance (Tandon et al., 1991). More specifically, it was proposed that muscarinic hyperactivity be associated to negative symptoms while decreased ACh neurotransmission be associated with positive symptoms (Tandon and Greden, 1989). This has provided the rationale for a growing number of studies to test the effectiveness of inhibitors of the acetylcholinesterase (AChE), i.e., cholinergic enhancers, in treating schizophrenia and related disorders.

Several studies in schizophrenia showed that various AChE inhibitors (e.g., galantamine, donepezil or rivastigmine) improve general symptom scores (Stryjer et al., 2003; Mendelsohn et al., 2004; Nelson et al., 2005a), negative symptoms (Deutsch et al., 2005) and depression (Nelson et al., 2005a). However, other studies showed no beneficial effects on symptoms (Tugal et al., 2004; Stip et al., 2004). As a matter of fact, it has been argued that alteration in the ACh activity in schizophrenia is more associated to cognitive deficits than to the expression of symptoms (Karson et al., 1993, 1996). It may also be that the effects are specific to a subpopulation of comorbid schizophrenia and dementia (Mendelsohn et al., 2004), or that the effects on symptoms are secondary to cognitive improvement. There are indeed an increasing number of studies showing that AChE inhibitors improve neuropsychological measures despite the stability of positive and negative symptoms. For instance, Kirrane et al. (2001) showed that physostigmine improved performance on a visuo-spatial working memory task in patients with schizotypal personality disorder. Similarly, studies using donepezil as an add-on treatment to risperidone, olanzapine or haloperidol showed improvement in verbal fluency, memory and processing speed (MacEwan et al., 2001; Buchanan et al., 2003; Kim et al., 2005). A recent open clinical trial with rivastigmine also showed an improvement of cognitive performance in schizophrenia patients treated with clozapine (Hussain et al., 2001). A recent meta-analysis indicates that ACh approach to enhance cognitive dysfunction in schizophrenia is viable (Friedman, 2004). Nevertheless, negative results have been obtained in some studies using donepezil (Friedman et al., 2002; Tugal et al., 2004) or rivastigmine (Chouinard et al., 2005). As suggested by Friedman et al. (2002), the discrepancies may rely on difference in the patient samples, particularly owing to tobacco use (i.e., nicotinic tolerance). They may also well rely on differences in the tools used to evaluate cognition as well as to the relative non-specificity of usual neuropsychological measures regarding cognitive processes and also regarding the distinct cholinergic systems which contribution to different aspects cognition is determined and constrained by their cortical projections.

In this respect, the recording of event-related potentials (ERPs) could be a useful alternative because they provide indices directly related to the neural activity underlying information processing during cognitive tasks. ERP abnormalities have long been reported in schizophrenia and they have also proven to be sensitive to various drugs, including those affecting ACh transmission. In healthy subjects, the muscarinic antagonist scopolamine affects ERPs (P3 component) as well as memory performance in the same way as it does following septo-hippocampal (Ch1) lesions in animals (Meador et al., 1987; Harrisson et al., 1988). More recently, it has been reported that the effect of ACh blockade on ERP is not topographically homogenous (Potter et al., 2000). It affects anterior (e.g., P3a) but not posterior (P3b) ERP components, a result that is more consistent with an effect on the nucleus basalis of Meynert (Ch4) system. Conversely and closely related to the present study, administration of ACh enhancers (i.e., donepezil or rivastigmine) in patients with Alzheimer's disease has been shown to reduce the P3 abnormalities proportionately to neuropsychological test improvements (Thomas et al., 2001). The relevance of these findings remains however limited, mostly because the studies used simple attention tasks (i.e., oddball) that are unlikely to capture adequately the full range of the cognitive processes in which ACh is involved, especially memory.

Over the past 15 years, numerous studies have investigated memory using ERPs and much progress has been made concerning the cognitive and neural interpretations of the components involved. The basic finding is an amplitude difference between the learning (new) and recognition (old) of items (Rugg and Doyle, 1994). In fact, this ERP old/new effect comprises several topographically distinct, though overlapping, components, each reflecting a specific process involved in memory (Friedman and Johnson, 2000; Guillem et al., 2001a). Several studies have described abnormalities of the ERP old/new effect in schizophrenia (Matsuoka et al., 1999; Matsumoto et al., 2001). Further, the various components of ERP old/new effect are affected in a differential manner, which represents a disturbance in the organization of information processing cascade (Guillem et al., 2001b, 2003). The various ERP anomalies are also related to symptoms in a differential manner, which provides a dynamic account of the cognitive mechanisms that lead to symptom expression (Guillem et al., 2003, 2005a). This study was thus designed to investigate the effect of an AChE inhibitor, i.e., rivastigmine, on memory ERPs in schizophrenia patients.

2. Methods

2.1. Participants

Eighteen patients gave informed consent to participate in this study. They had a DSM-IV (APA, 1994) diagnosis of schizophrenia and cognitive deficits defined as a score lower than 90 on both the immediate and delayed memory indices of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, 1998). This score was established according to the norms in healthy individuals which varies from 90.8 to 102.9 on memory index depending of the scholarship and data obtained in schizophrenia patients who have a mean of 73.8 on immediate memory and 74.9 on delayed memory index. Patients presenting other DSM Axis I or III diagnoses, especially drug abuse (amphetamines, ecstasy, PCP, cocaine, THC or alcohol), or pronounced suicidal potential were excluded from the study. They filled the Fagerström Test for

Nicotine Dependence (FTND) (Heatherton et al., 1991; Pomerleau et al., 1994) to control for potential group difference on this variable. Patients presenting a known hypersensitivity to rivastigmine, other carbamates or ingredients in the formulation were not included either. All the patients had a normal or corrected-to normal vision to be able to perform the visual memory task. They were all medicated with atypical antipsychotic at the time of enrolment. The dose of antipsychotic and the type of adjunct medication were documented throughout the trial. The patient characteristics are presented in Table 1.

2.2. Study design

The design was a randomized crossover trial, not placebo-controlled, in which patients were evaluated first at baseline (T1) and on two subsequent occasions (T2 and T3) at 12-week intervals. The initial evaluation was carried out to establish baseline values. Then, half of the participants were randomly assigned to rivastigmine co-administrated with their antipsychotic (G1) for a 12-week period, whereas the other half (G2) still receive their current medication. All the patients were evaluated for T2 at the end of this period and treatment group assignments were then reversed, i.e., G1 stopped receiving rivastigmine, whereas G2 started receiving rivastigmine for 12 weeks. All the patients were evaluated for T3 the end of this period.

Table 1
Subjects' characteristics (S.D. in parentheses)

	G1 (N=9)	G2 (N=9)
Sex (M/F)	6/3	8/1
Age (years)	32.7 (8.6)	25.1 (4.9)
Educational level achieved[a]	2.2 (0.5)	2.0 (0.0)
Age at onset (years)	24.1 (4.0)	21.4 (1.6)
Fagerström Test (FTND)	3.8 (3.9)	3.9 (3.3)
Symptoms		
PANSS total score at T1	73.4 (6.8)	75.1 (7.8)
Dimensional scores at T1		
Negative	14.3 (3.7)	15.9 (6.3)
Positive	20.4 (4.8)	20.3 (2.1)
Disorganization/cognitive	11.7 (1.7)	11.7 (2.2)
Hostility/excitement	14.4 (2.4)	13.8 (2.3)
Anxiety/depressive	9.0 (1.9)	9.4 (1.7)
RBANS score at T1	69.9 (8.1)	69.4 (10.9)
Immediate memory	69.4 (11.4)	68.3 (11.3)
Delayed memory	71.9 (14.2)	57.9 (15.7)
Antipsychotic dose (eq 100 mg CPZ/day)		
T1	4.6 (4.5)	6.4 (9.0)
T2	5.2 (5.0)	6.4 (9.0)
T3	5.2 (5.0)	6.5 (9.0)
Adjunct medications (no. of patients)		
Anxiolytics	4	1
Antidepressants	4	3
Thymoregulators (Li)	2	0
Antiparkinsonians	3	2
Anticonvulsivants	4	2

[a] Educational level is quoted from 1 to 5 (1=grade school, 2=high school, 3=bachelor, 4=master, 5=PhD).

Table 2
Individual items' constitution of the five PANSS dimensions according to Lançon et al. (1997)

Dimension	Item
Negative	Excitement (P4)
	Blunted affect (N1)
	Emotional withdrawal (N2)
	Poor rapport (N3)
	Passive/apathetic social withdrawal (N4)
	Lack of spontaneity and flow of conversation (N6)
	Motor retardation (G7)
	Active social avoidance (G16)
Positive	Delusions (P1)
	Hallucinatory behavior (P3)
	Grandiosity (P5)
	Suspiciousness/persecution (P6)
	Somatic concern (G1)
	Guilt feelings (G3)
	Depression (G6)
Disorganization/cognitive	Conceptual disorganization (P2)
	Difficulty in abstract thinking (N5)
	Disorientation (G10)
	Poor attention (G11)
	Poor impulse control (G14)
Hostility/excitement	Hostility (P7)
	Uncooperativeness (G8)
	Unusual thought content (G9)
	Lack of judgment and insight (G12)
	Disturbance of volition (G13)
	Preoccupation (G15)
Anxiety/depressive	Stereotyped thinking (N7)
	Anxiety (G2)
	Tension (G4)
	Mannerisms and posturing (G5)

2.3. Rivastigmine adjunctive treatment

The rivastigmine was administered 1.5 mg twice a day p.o. for 4 weeks, then the daily dose was increased by 3 mg twice a day for the next 4 weeks so as to reach 6 to 9 mg daily for the last 4 weeks depending tolerability of patients. Maintenance dose in other diseases ranges from 3 to 6 mg twice a day taken with a full meal in the morning and the evening. Titration in this trial was mildly inferior to that usually recommended for an elderly population because a young population can be expected to be more sensitive to stop medication if they experience nausea and vomiting.

2.4. Symptom assessment

At every evaluation session, patients were assessed for clinical symptoms using the French version of the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987; Lépine, 1996) by one trained rater blind to the treatment. Item scores were also summarized as dimensional scores according to the validation study of the French version of the PANSS (Lançon et al., 1997). The model comprises five dimensions comparable to those defined by Kay and Sevy (1990): negative, positive, disorganization/cognitive, hostility/excitement and anxiety/depressive (Table 2).

2.5. ERP recordings and extraction

At each evaluation session, ERPs were recorded during a memory task for unfamiliar faces similar to the that extensively used in to explore memory in healthy subjects and successfully evidence ERP correlates of memory impairments in schizophrenia (Guillem et al., 2001a,b, 2003). The protocol was based on a classical 'continuous recognition task' design. Participants were presented with a stimulus sequence in which items occurring a first time (new) reappeared subsequently once (old) after 2 to 20 intervening items. On each trial, they had to decide, as fast and accurately as possible, whether the item has been previously presented (old) or not (new) by pressing keys on a computer keyboard. A practice session using faces not included in the test blocks was performed prior to the test in order to familiarize the subject with the task. The stimuli were color front views of unfamiliar faces taken from the MED bank of faces (Debruille et al., 1997) distributed across three different blocks each comprising 73 stimuli on 146 trials. The order of the three blocks was counterbalanced across subjects and subjects rested for 5 min between each block. Different series of blocks were used across the three sessions. During the test session, subjects were seated in front of a computer monitor placed 1.5 m away. Faces were presented for 500 ms with an ISI varying randomly between 2.5 and 3.5 s (mean = 3.0, S.D. = 0.4).

EEG was recorded from 13 scalp sites according to the 10–20 system (midline: Cz, Pz, lateral: FP1, FP2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, O2) referenced to linked earlobes. Eye movements and blinks (EOG) were monitored via electrodes placed below and on the outer canthus of the left and right eyes. Impedance of all electrodes was set below 5 kΩ. Continuous EEG (0.01–30 Hz bandpass) was digitized on-line (256 Hz) and averaged off-line after EOG correction using statistical software algorithms. ERPs were computed from 0- to 1000-ms post-onset with a 200-ms pre-stimulus baseline for new and old items. Only ERPs associated with correct responses were analyzed. ERP peaks were identified by visual inspection of the individual traces recorded at Cz within the 200–800-ms post-onset. This epoch was selected as typical for previous studies of the ERP old/new effect. Amplitudes were quantified with respect to the 200-ms pre-stimulus baseline within several time windows. For each peak, the lower limit of the time window was defined as the median latency between the current and the previous peak. The upper limit corresponded to the median latency between the current and the following peak. This procedure resulted in non-overlapping time window of varying duration that allow to capture amplitude effects separately for each peak (Guillem et al., 2001a,b). As in previous studies using the same protocol, four peaks were identified: N300 (214–315 ms), P350 (315–423 ms), N500 (423–574 ms) and P700 (574–853 ms).

2.6. Statistical analysis

Clinical data were first analyzed at T1 to detect potential group differences at baseline using Student's *t*-test. For the trial, the data were analyzed using mixed ANOVA models with the 'group' (G1 vs. G2) (and as between-subjects factor and the session T2 vs. T3) as within-subject variable to determine the influence of rivastigmine treatment, i.e., a group×session interaction.

Scores (% correct responses and % false alarms) for the memory task were similarly analyzed for T1 analyzed using Student's *t*-test and for the trial using a group×session mixed ANOVA models. Reaction times (RTs) were compared using ANOVAs with the group as between-subjects factor and session and 'condition' (old vs. new) as within-subject variables.

ERP data were analyzed separately for midline and lateral sites using mixed ANOVA models. For T1 data, the model included the group as a between-subject factor, the condition and electrode 'site' as within-subject variables for the midline data or the site and laterality (left vs. right) for the lateral sites. The trial data were analyzed using similar model with the additional variable of session. In all analyses, degrees of freedom were adjusted using the Huynh-Feldt procedure where appropriate (uncorrected *df* are reported with the epsilon, ε values and corrected *p*-values). Since this study aimed at investigating the effect of rivastigmine, the analysis of the data obtained during the trial (i.e., T2, T3) primarily focused on interactions involving the factors of group and session. Other effects are mentioned only if they are relevant to understand and further discuss the results, e.g., by distinguishing topographically distinct ERP components.

In case of significant effect of group or interaction involving this factor were evidenced at baseline (T1) on a given variable, the baseline values were entered as a covariate in the trial analysis (T2 vs. T3).

Two tailed Pearson's correlations were further used to investigate the potential relationships of behavioral and ERP measures with the dimensional scores obtained from the PANSS. Correlation analyses were carried out separately for patients who were receiving rivastigmine (i.e., G1 at T2 and G2 at T3) and for those who were not (i.e., G1 at T3 and G2 at T2). The behavioral and ERP measures entered in the analyses were selected according to the results from the previous ANOVAs.

3. Results

3.1. Epidemiological and clinical data

The comparison between the two patients groups at baseline (T1) showed no difference between groups in sex distribution, educational level, age at the onset of the illness and FTND score. There was a significant group difference in age [$F(1,16) = 5.48$, $p = 0.03$] that was due to one subject aged 50 in G1. This difference was not considered as critical since the effect of rivastigmine was assessed in a within-subject design.

There was no difference on the global severity of illness (PANSS total score), on the dimensional scores or on the RBANS data. There was also no group difference, at baseline, in the antipsychotic dose as well as on the nicotinic dependence score.

Table 3
Symptom ratings during the trial (S.D. in parentheses)

	G1 (*N*=9)		G2 (*N*=9)	
	T2	T3	T2	T3
PANSS total score	73.7 (7.8)	72.4 (9.4)	71.9 (5.6)	73.1 (5.7)
PANSS dimensional scores				
Negative	14.7 (2.7)	12.6 (5.1)	15.3 (4.7)	15.8 (4.9)
Positive	20.4 (4.9)	18.1 (8.2)	19.3 (2.8)	18.6 (3.5)
Disorganization/cognitive	11.7 (3.2)	9.9 (4.3)	11.2 (2.2)	12.0 (1.8)
Hostility/excitement	14.2 (1.8)	13.4 (5.5)	14.0 (2.0)	14.6 (1.7)
Anxiety/depressive	8.9 (0.9)	7.9 (3.3)	8.9 (1.1)	8.4 (1.1)

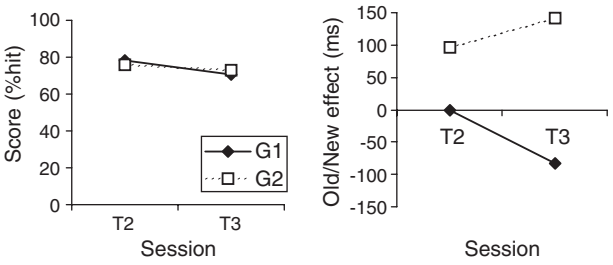

Fig. 2. Behavioral performance during the trial (left: accuracy scores, right: repetition effect (old–new difference)).

The analysis on the PANSS and dimensional scores at trial (Table 3) also revealed no significant effect of group, session or interaction between the two factors.

3.2. Behavioral data

The analysis of the accuracy score (% correct) revealed no significant effects for both the baseline (Fig. 1) and the trial data (Fig. 2), indicating that rivastigmine treatment has no beneficial effect on this measure. The ANOVA on the RT data obtained at baseline (T1) showed a trend toward significance for the group×condition interaction [$F(1,16)=3.27$, $p=0.08$]. This result corresponds to the observation that although G1 patients are generally faster than those from G2 (mean RTs: G1=1449.3 ms. G2=2128.8 ms), they have lower repetition effect (i.e., new–old difference) (Fig. 1). The ANOVA on the trial data controlling for this difference showed a significant effect of group [$F(1,15)=4.38$, $p=0.05$], a significant group×-condition interaction [$F(1,15)=5.30$, $p=0.04$] and a trend for a group×session×condition interaction [$F(1,15)=3.34$, $p=0.08$]. Fig. 2 shows that this result represents the larger repetition (old/new) effect when patients from both groups received rivastigmine (i.e., T2 for G1 and T3 for G2).

3.3. ERP data

The typical grand average waveforms show four peaks similar to those previously reported in the same task in healthy and schizophrenia subjects (Guillem et al., 2001a,b). For all the four time windows, ANOVAs on the T1 data from the midline and lateral ERPs revealed the effects of condition, site and/or interaction between the two factors usually reported in such studies but there was no significant group effect or interaction involving this factors to indicate baseline difference. Thus, these data will not be discussed further and the following presents only the results obtained from the trial (i.e., T2 and T3).

3.3.1. N300 time window (214–315 ms)

The ANOVAs on both the midline and lateral data resulted in a significant group×session interaction [midline: $F(1,16)=4.16$, $p=0.05$; lateral: $F(1,16)=5.97$, $p=0.02$] indicating an effect of rivastigmine on ERP amplitude in the N300 time window. Fig. 2 shows that this effect reflects the more positive ERPs in patients receiving rivastigmine (i.e., T2 for G1 and T3 for G2).

There were also significant effects of condition [midline: $F(1,16)=51.40$, $p=0.02$; lateral: $F(1,16)=4.22$, $p=0.05$] and site [midline: $F(1,16)=23.67$, $p<0.001$; lateral: $F(7,112)=27.51$, $p<0.001$, $\varepsilon=0.259$] and the analysis on lateral data revealed an additional site×laterality [$F(7,112)=2.34$, $p=0.04$, $\varepsilon=0.548$]. These results reflect the differential distribution of ERPs over left and right hemisphere and over frontal and posteriors sites. Fig. 3 shows that this distribution is related to the distinction between the frontal P2a and the posterior temporal N2b (or N300) described in previous studies in healthy and schizophrenia subjects (Potts and Tucker, 2001; Potts et al., 2002; Guillem et al., 2003).

3.3.2. P350 time window (315–423 ms)

The ANOVAs on the midline data resulted in a significant group×session interaction [$F(1,16)=4.68$, $p=0.04$]. There were also a significant effects of condition [$F(1,16)=5.96$, $p=0.03$]

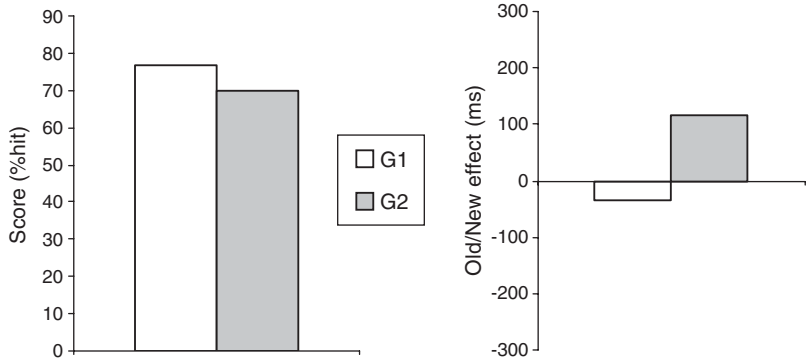

Fig. 1. Behavioral performance at baseline (left: accuracy scores, right: repetition effect (old–new difference)).

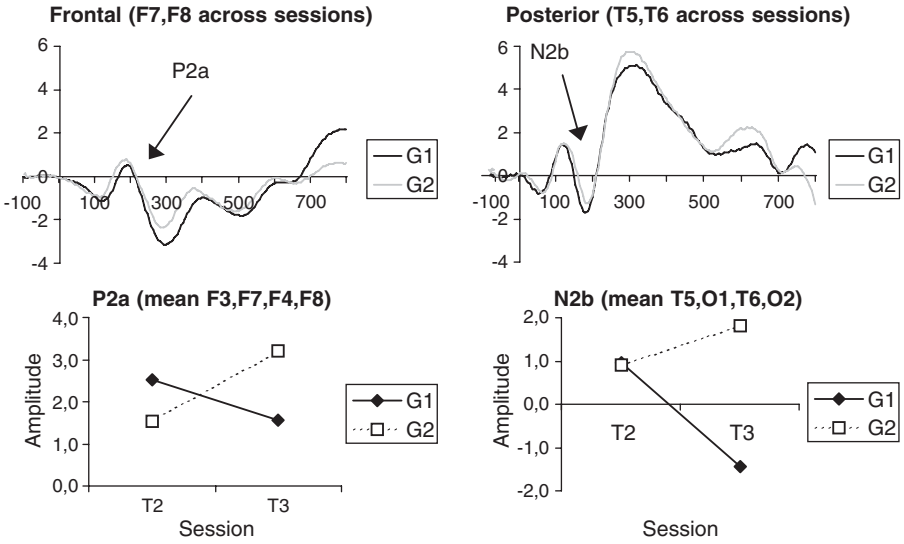

Fig. 3. ERPs averaged across sessions and conditions over frontal (left) and posterior temporal (right) sites and respective amplitude measures (lower panels) within 214–315 ms.

and site [$F(1,16)=31.10$, $p<0.001$] and a significant interaction between the two factors [$F(7,16)=6.06$, $p=0.02$]. The ANOVAs on the lateral data showed significant group×session [$F(1,16)=6.24$, $p=0.02$] and a trend toward significance for a group×session×condition interaction [$F(1,16)=3.74$, $p=0.07$]. There was also a significant effect of site [$F(7,112)=16.42$, $p<0.001$, $\varepsilon=0.407$] and a trend toward a group×condition×site interaction [$F(7,112)=2.20$, $p=0.07$, $\varepsilon=0.673$]. These results indicate that rivastigmine affects the ERP amplitude within this time window and also tends to affect their modulation, i.e., the ERP old/new effect. The ERP old/new effect also shows a trend to be differentially distributed over the scalp. As argued elsewhere, these results likely reflect the beginning of the ERP old/new effect that reach its maximum in the N500 time window and decrease during the P700 (Guillem et al., 2001b, 2003; see below).

3.3.3. N500 time window (423–574 ms)

The ANOVAs on both the midline and lateral data resulted in a significant group×session×condition interaction [midline: $F(1,16)=6.48$, $p=0.02$; lateral: $F(1,16)=6.17$, $p=0.02$] indicating that rivastigmine affects the ERP old/new effect in the N500 time window. Fig. 3 shows that lager old/new effect is elicited in patients receiving rivastigmine (i.e., T2 for G1 and T3 for G2). The ANOVAs also revealed significant effects of site [midline: $F(1,16)=13.65$, $p=0.002$; lateral: $F(7,112)=3.52$, $p=0.02$, $\varepsilon=0.470$] and condition [midline: $F(1,16)=5.08$, $p=0.04$] as well as significant interactions between the two factors [midline: $F(1,16)=5.11$, $p=0.04$; lateral: $F(7,112)=2.55$, $p=0.04$, $\varepsilon=0.647$]. These results indicate the differential modulation of ERPs over the scalp often reported to reflect the presence of two dissociable components. One with frontal topography has been variously termed FC (Guillem et al., 2001a,b, 2003) or F-N400 (Mecklinger, 1998; Curran, 1999) to distinguish it from the other, i.e., the well-documented parietal N400 (Fig. 4).

3.3.4. P700 time window (574–853 ms)

ANOVAs revealed no significant effect involving a group×session interaction. This result indicates that rivastigmine does not influence the P700 component or its modulation. There were however significant effects or trends for the factors of condition [midline: $F(1,16)=5.87$, $p=0.03$), site [lateral: $F(7,112)=4.07$, $p=0.006$, $\varepsilon=0.570$] and trends for the interaction between the two factors [midline: $F(1,16)=4.15$, $p=0.06$; lateral: $F(7,112)=2.55$, $p=0.09$, $\varepsilon=0.547$]. Analysis on lateral data also shows a significant site×laterality interaction [$F(7,112)=5.38$, $p=0.007$, $\varepsilon=0.334$]. These results reflect the right posterior distribution of the P700 described in previous studies (Guillem et al., 2003).

3.4. Correlation with symptoms

The correlation analysis showed no significant association between the dimensional scores and the behavioral memory effect (i.e., old minus new difference).

For ERPs recorded within the N300 time window, summary measures were calculated as the mean amplitude across condition because there was no significant effect of this factor in the previous ANOVAs. Correlations were computed for selected posterior (T5, O1, T6, O2) and frontal sites (F3, F7, F4, F8) to take into account the distinction between P2a and N2 components. For ERPs recorded within the N300 time window, summary measures were calculated as the mean the ERP memory effect (i.e., old minus new difference) because this factor interacted with group and session in the previous ANOVAs. Correlations were computed for selected parietal (C3, P3 C4, P4) and frontal sites (F3, F7, F4, F8) to take into account the distinction between N400 and F-N400 components. Although the previous analysis did not show any effect of rivastigmine within the P700 time window, a correlation analysis on this component was also carried out because its amplitude, or its modulation, has been reported associated with

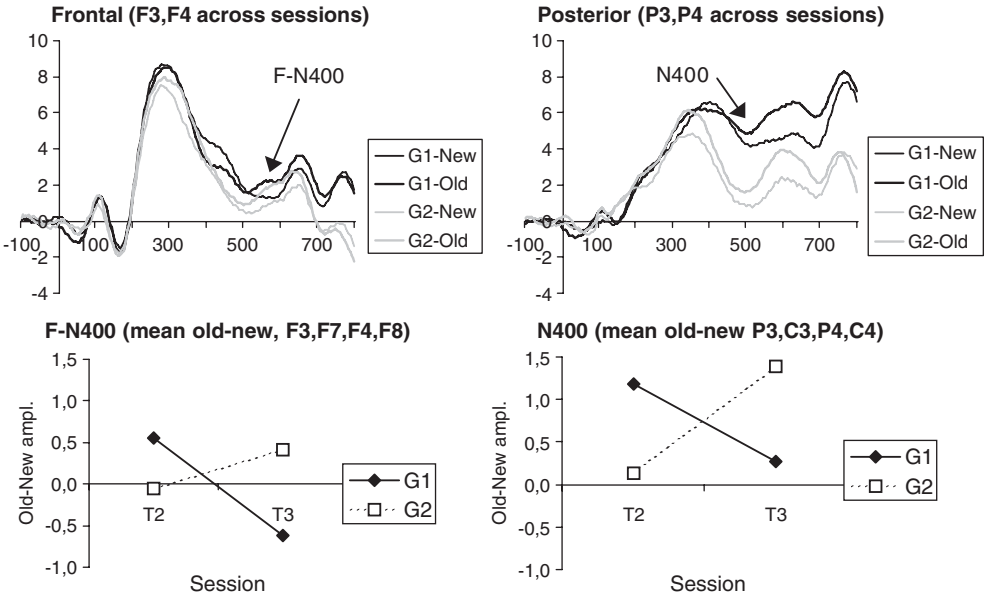

Fig. 4. ERPs averaged across sessions over frontal (left) and parietal (right) sites and respective repetition effects (lower panels) within 423–574 ms.

symptoms (Guillem et al., 2001b, 2003). The analysis for this component was made in the same way and for the same sites as for the N500 time window.

The results of the correlation analysis between dimensional scores and ERP measures are presented in Table 4. To summarize, the results showed significant positive correlations between the left posterior N2 and positive symptoms in both patients receiving and not receiving rivastigmine. This component also correlates positively with anxiety/depressive symptoms in patients without rivastigmine only. A positive correlation between the right posterior N2 and negative symptoms was also found in patients without rivastigmine. The analysis of ERPs in the N500 time window revealed significant associations only in patients receiving rivastigmine. Although all these correlations were positive, a distinction can be made between the F-N400 that tend to be associated with positive symptoms and the parietal N400 associated with hostility/excitement. Finally, ERPs in the P700 time window revealed significant associations in patients not receiving rivastigmine only. Noteworthy, these associations involve all the symptoms dimensions except the positive symptoms, are widely distributed across the scalp and are all negative correlations.

4. Discussion

4.1. Rivastigmine and symptoms

The first result of this study is that rivastigmine appears not to have any effects on symptoms measures. This result, a priori,

Table 4
Correlation with symptoms

	With rivastigmine (G1/T2 and G2/T3)			Without rivastigmine (G1/T3 and G2/T2)		
	Amplitude 214–315 ms	Old/new effect 423–574 ms	Old/new effect 574–853 ms	Amplitude 214–315 ms	Old/new effect 423–574 ms	Old/new effect 574–853 ms
Negative				T6 (0.44)†		F4 (−0.52)* F8 (−0.61)**
Positive	T5 (0.48)*	F8 (0.46)†		T5 (0.54)*		
Disorganization/cognitive						F4 (−0.72)** F8 (−0.54)* C4 (−0.57)** P4 (−0.53)**
Hostility/excitement		C4 (0.49)* P4 (0.44)†				F4 (−0.6)** P3 (−0.50)* P4 (−0.51)*
Anxiety/depressive			C3 (0.56)** P3 (0.46)*	T5 (0.53)*		F4 (−0.50)*

†Trend: $p=0.06$, *$p \leq 0.05$, **$p \leq 0.01$.

does neither support that ACh hyperactivity (induced by rivastigmine) contributes to the expression of negative symptoms or that a ACh hypoactivity (reduced by rivastigmine) contributes to positive symptoms (Tandon and Greden, 1989). If so, one would have observed a worsening of negative symptoms and an improvement in positive symptoms. However, it is worth to note that the ACh is likely to contribute to positive symptom expression by permitting dopamine (DA) hyperactivity (Tandon and Greden, 1989). In this study, rivastigmine was added on the patients' current antipsychotic medications, which primary action as DA antagonists precisely aims at reducing the DA hyperactivity that underlie positive symptoms. Furthermore, patients were receiving only atypical compounds, whose wide spectrum of antagonistic, including ACh, action, is supposed to contribute to their relative better efficacy on negative symptoms and cognition (Tamminga, 1997). This may explain why rivastigmine co-administration, especially at the low doses used here, adds nothing to the effects of antipsychotics on symptoms. More importantly for the present purpose, this also rules out the possibility of any cognitive effects described subsequently to be related to indirect effect through symptom improvement.

4.2. Rivastigmine effects on behavioral measures

Similar to the literature on the cognitive effects of ACh enhancers in schizophrenia (see Introduction), the present behavioral results are mixed. Rivastigmine appears to have no effect of on accuracy score, but it induces a slight amelioration on RT measures of the old/new effect. In a first approximation, this would indicate that rivastigmine does not have a homogeneous action on cognition. Rather, it seems to improve some processes, without affecting others. As a matter of fact, it has long been argued that accuracy score and RT reflect distinct aspects of memory processing (MacLeod and Nelson, 1984). Accuracy score relates to qualitative aspects of information retrieval, i.e., to the accessibility or elaboration of the information in memory, whereas RT relates to its quantitative aspects, i.e., to the effort required to retrieve the information. By this view, our results indicate that rivastigmine may favor the quantitative aspects of retrieval, i.e., an easier discrimination between old and new items, but not the accessibility of the information in memory. This is consistent with studies showing that impairments of visual attention and discriminative accuracy are attributable to ACh deficits (Marston et al., 1994; Muir et al., 1994). Furthermore, to the extent that better memory discrimination reflects better consolidation, the results are also consistent with the role of ACh in consolidation (Flood et al., 1984), likely through its facilitatory action long-term potentiation (LTP) (Tanaka et al., 1989; Blitzer et al., 1990).

4.3. Rivastigmine effects on memory ERPs

Generally, the results show that rivastigmine affects ERP components in differential manner. This observation that parallels the behavioral results should be taken as evidence that the effects of rivastigmine on memory is not unitary, but comes from its action at different time points within information processing cascade.

On early components, the effect is twofold. First, rivastigmine increases the frontal P2a. This component thought to reflect stimulus salience processing and interference inhibition is usually found reduced in schizophrenia (Potts and Tucker, 2001; Potts et al., 2002; Guillem et al., 2003). On the other hand, rivastigmine reduces a posterior temporal negativity that corresponds to the N2b. This component is usually associated with categorization and its amplitude reflects the reactivity to the incoming stimulus. In schizophrenia, larger N2s have been associated to paranoid or reality distortion symptoms (Oades et al., 1994; Bruder et al., 2001; Guillem et al., 2003). Thus, following these interpretations, the present results indicate that rivastigmine enhances interference inhibition (P2a) and decreases the reactivity to incoming stimulus (N2b). Because the combination of these two mechanisms would necessarily result in increasing the signal to noise ratio, the results suggest that rivastigmine improves patients' selective attention. Consistent with the role of ACh in visual attention and discrimination (Marston et al., 1994; Muir et al., 1994), this could partly account for behavioral effect described above. Possibly, this effect could be mediated by the action of rivastigmine on the basal nucleus of Meynert system (Ch4) that has been involved in the selection of task-relevant information (Everitt and Robbins, 1997). This idea is supported by the fact that, anatomically, this system targets the orbitofrontal and inferior posterior cortices in which the P2a and N2 are thought to be generated, respectively (Potts and Tucker, 2001, Potts et al., 2002, Guillem et al., 2001a,b, 2003). It is also in agreement with fMRI studies showing that rivastigmine increases activation in the fusiform gyrus and prefrontal cortex during face encoding and simple working memory tasks (Rombouts et al., 2002).

Another complex effect of rivastigmine occurs later, within 423–574-ms post-stimulus onset that encompasses two distinct components. The frontally distributed one has been often referred to as the F-N400 (Mecklinger, 1998; Curran, 1999) and its old/new modulation to the FC effect (Guillem et al., 2001a, b). It has been generally associated with contextual processing (Wilding et al., 1995; Senkfor and Van Petten, 1998). More specifically, in the context of old/new decision tasks, the more positive amplitude to old stimuli has been related to the processing of contextual information encoded with the stimulus (Guillem et al., 2001a). The posteriorly distributed N500 component is a variant of the classical parietal N400 elicited in face recognition tasks. The general consensus is that its amplitude relates to the ease with which information is integrated with personal knowledge (Holcomb, 1993) and that its modulation in old/new decision tasks reflects the easier integration of old stimuli compared to new ones (Rugg and Doyle, 1994). Following these interpretations, the increased effects observed in patients receiving rivastigmine indicate that co-administration enhances the integration of information with knowledge (N400) and the processing of contextual information (F-N400). This view is supported by the finding that AChE inhibitors increase the metabolic activity in the prefrontal cortex

(Risch et al., 2001; Kaasinen et al., 2002; Nahas et al., 2003; Saykin et al., 2004) and that the prefrontal cortex regulates ACh release in posterior parietal areas (Nelson et al., 2005b). Noteworthy, this combination is exactly what can be expected when the representation of information becomes more abstract or consolidates in memory. The link between these effect recorded on the scalp and consolidation is also supported by intracranial recording studies showing that N400 corresponds to a period of neural excitation that may favor LTP (Heit et al., 1988; Halgren, 1990). To the extent that consolidation would enhance the discriminability between old and new stimuli, this mechanism could also contribute to the behavioral effect on RT only. On an anatomical viewpoint, this effect of rivastigmine could be mediated by its action on the diagonal band system (Ch2–3) that has been involved in the learning and retrieval of associations (Everitt and Robbins, 1997). Again, the idea is supported by the fact that this system targets dorsolateral prefrontal and posterior associative neocortical areas that corresponds to those where the F-N400 and N400 are generated, respectively (Nenov et al., 1991; Rugg et al., 1996; Guillem et al., 1999).

Finally, the present study does not show any effects of rivastigmine on the late positive component here termed P700. This component likely corresponds to the P600 or LPC in other studies where it has been associated to elaboration or, more specifically, to a 'mnemonic binding' process that links separate aspects of information into a coherent representation (Van Petten et al., 1991; Rugg and Doyle, 1994). Therefore, the present results indicate that rivastigmine does not act on this processing stage. Since the P600 reflects qualitative aspect of memory representations such as elaboration or its accessibility determined by mnemonic binding, this observation could account for lack of effects on this accuracy score. The results further suggest that rivastigmine does not affect the septo-hippocampal system (Ch1) involved in the binding processes reflected in the P600 effect (Everitt and Robbins, 1997), at least with the low doses used here.

4.4. Differential symptoms–ERP relationships in patients with or without rivastigmine

A first result of the correlation analysis is the presence of an association between the N2 amplitude over the right hemisphere and the negative symptom score when patients did not receive rivastigmine. The positive direction of the correlation indicates that N2 decreases (i.e., becomes more positive) when negative symptoms increase. This result is thus similar to association found between this component and blunting (El Massioui and Lesèvre, 1988; Pelosi et al., 2000), which could reflect an hyporeactivity to emotional stimuli (Guillem et al., 2003, 2005a). The fact that this association is not present in patients receiving rivastigmine indicates that co-administration modifies the relationship between blunting and hyporeactivity. This observation is reminiscent to some reports that cognitive enhancer (i.e., donepezil) improves depression in schizophrenia (Risch et al., 2001; Nelson et al., 2005a). On the other hand, the results showed an association between N2 amplitude over the left hemisphere and positive symptoms whether the patients were receiving rivastigmine or not. Such an association between the left N2 and positive symptoms has been already reported in other studies (Oades et al., 1994; Bruder et al., 2001; Guillem et al., 2003), but in the opposite direction. Thus, even though the significance of the present result is unclear, the relevant point here is that the association is not modified by rivastigmine.

More interesting is that rivastigmine induces an association between the N400 modulation and the excitement/hostility score that was absent in patients who were not receiving the medication. The positive direction of the association indicates that the improvement of integrative processes reflected in the N400 modulation with rivastigmine also favors the expression of excitement/hostility symptoms, e.g., unusual thoughts, lack of judgment and preoccupation (Table 2). Rivastigmine also tends to induce a positive relationship between the F-N400 modulation and positive symptom scores. This association is somewhat similar to the report of a larger frontal effect in patients with high reality distortion, in whom it has been attributed to overprocessing of intrinsic contextual information (Guillem et al., 2003). Thus, the present result could indicate that rivastigmine favors this overprocessing. Finally, the correlations in the P600 time window show rather different pattern depending on the patients were receiving rivastigmine or not. In those not receiving the medication, ERP modulation show a wide pattern of negative associations involving various anterior and posterior sites and all the symptom dimensions, except positive symptoms. To the extent that the P600 is a memory counterpart of the classical P3 (Van Petten et al., 1991), the present observation is in agreement with the assumption that the reduction of the visual P3 is a general state marker of schizophrenia (Duncan et al., 1987; Mathalon et al., 2000). It does not appear to be the case when patients receive rivastigmine, as if P600 was no more a state maker. In these patients, the old/new modulation of the left posterior P600 increases with anxiety/depression symptoms. Interestingly, recent findings from a study of the P600 in reality distortion patients (Guillem et al., 2003) and the observation of an association of the P600 old/new effect with trait anxiety (Guillem et al., 2005a) led to the conclusion that, in schizophrenia, it represents an inappropriate mnemonic binding or the attribution bias by which subjects tend to resolve anxiety. In this case, the present results would indicate that rivastigmine favors such an attribution bias.

4.5. General remark

Generally, the present study shows that rivastigmine add-on therapy may act as a cognitive enhancer by improving some specific stages in the information processing cascade. However, it should be acknowledged that the combination of the three major effects associated to rivastigmine, i.e., (1) decreasing the reactivity to incoming stimulus (N2b), (2) overprocessing of intrinsic contextual information (F-N400) and (3) increasing knowledge integration or consolidation (N400), is likely to favor an introverted or neurotic cognitive functioning. This idea

is supported by the fact that neuroticism comprises self-preoccupation and uncooperativeness features (Eysenck and Eysenck, 1985) similar to the symptoms included in the excitement/hostility dimension associated with increased N400 effect. Neuroticism is also associated to some degree of emotional instability, anxiety and worry, similar to the symptoms included in the anxiety/depression dimension that is associated with increased P600 effect. It is also worth noting that higher level of positive symptoms has been associated with higher level of neuroticism (Lysaker et al., 1999) as well as of depression and anxiety (Norman et al., 1998; Guillem et al., 2005b).

5. Conclusion

In summary, our study suggest that co-administration of rivastigmine in schizophrenia is double-edged. On one hand, it could actually enhance cognition, but, at the same time, it could favor a neurotic functioning, which in turn may induce the expression of positive symptoms. This is in agreement with the proposal that ACh hypoactivity is characteristic of the chronic state, whereas ACh hyperactivity is more contributing to positive symptoms and the acute state of the illness (Tracy et al., 2001). By increasing ACh availability, rivastigmine may progressively convey the ACh hyperactivity observed in the acute state. Therefore, even though rivastigmine may have beneficial effects on memory in schizophrenia, the present findings also advises to the greatest caution upon the doses and the type of patients in whom it is administered at the risk of relapse. In any case, the potential beneficial effects vs. risks of ACh enhancers, such as rivastigmine, may be worth to be investigated further in placebo-controlled trials on larger patient samples.

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