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Action verb understanding in first-episode schizophrenia: Is there evidence for a simulation deficit?

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ABSTRACT

Schizophrenia is often associated with deficits in the domain of language, which are thought to be closely related to deficits in the structure of semantic knowledge. The main aim of the present study was to behaviorally investigate whether semantic impairments in schizophrenia are present also at the very basic level of action verb processing, in particular at the level of motor simulation. We used a go-no go paradigm both for a semantic decision task (with either an early, EGD, or a delayed go-signal delivery, DGD) and for a lexical decision task (control task). Only the first task requires motor simulation to be solved. We found that first-episode schizophrenia (FES) patients, like healthy control (HC) participants, use motor simulation as a basic strategy to semantically judge action verbs. In the EGD condition, both motor simulation and action verb understanding seem to be preserved in FES. However, differently from HC participants, FES patients kept on using the simulation strategy also with the DGD condition, whereas, simultaneously, task performance during this condition appeared to be less efficient and sensitive. Voxel-based morphometry analysis suggested that this altered performance in FES patients could be related to structural brain abnormalities in the right dorsolateral prefrontal cortex. We propose that a prolonged motor simulation in FES may serve as a compensatory strategy for impairments in the selection of action representation and/or for memory deficits disclosed by the DGD condition during the semantic decision task investigated in the present study.

1. Introduction

Symptoms of schizophrenia reflect abnormalities in multiple aspects of human thought, language, and communication. Disturbance of language is among the first clinical features described for this syndrome (Bleuler, 1950; Kraepelin, 1904) and is considered by some authors as fundamental to its etiology (Crow, 1997). Bleuler conceived schizophrenia as a syndrome characterized by a disturbance of associations, reflected in a breakdown in putative associative threads that serve to interweave words, thoughts, and ideas into coherent discourse. According to this view, he proposed that the study of language processing can contribute to a better understanding of the neuropathology of schizophrenia as a whole (Bleuler, 1950). Likewise, Andreasen considered the observation of language behavior as a way of evaluating thought disorders and developed a rating scale appropriate for the assessment of these aspects (Andreasen, 1979). More recent empirical evidence suggests that language processing impairments in schizophrenic patients are related to other aspects of psychotic thought and behavior, including delusions (Holt et al., 2006), hallucinations (Ditman & Kuperberg, 2005), non-goal-directed behavior (Sitnikova, Goff, & Kuperberg, 2009), and negative symptoms (Kuperberg, Kreher, Swain, Goff, & Holt, 2011). Moreover, it has been proposed that language impairments in patients with schizophrenia may be associated with specific deficits in the structure of semantic knowledge (Chen, Wilkins, & McKenna, 1994; Paulsen et al., 1996; Rossell & David, 2006).

The deficits found in semantic processing, fluency and complexity (e.g., Kareken, Moberg, & Gur, 1996; Rochester & Martin, 1979; Thomas et al., 1996), have been considered the most interesting

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ones, because they are likely related to the organization of language in the cerebral cortex (DeLisi, 2001). Kuperberg and Colleagues (2008) investigated the neural underpinnings of building meaning from language in schizophrenia referring to two types of processes: a semantic memory-based process, which consists in activating, retrieving and matching stored semantic information with incoming material, and a semantic integration process. The first one could be more dependent on inferior frontal and temporal processes, whereas the second one could additionally recruit the dorsolateral prefrontal cortex (DLPFC) and sometimes parietal cortices. To this aim, they contrasted words within sentences that were (1) either concrete or abstract and (2) either semantically incongruous or congruous with their preceding contexts. In both contrasts patients failed to recruit the DLPFC. In addition, the second contrast revealed that patients also failed to recruit medial frontal and parietal cortices. These results led the authors to suggest that dysfunction during the construction of higher-order meaning in schizophrenia is best conceived of as a disturbance in the balance between semantic memory-based and integrative mechanisms. Patients may be relatively more dependent on semantic memory-based processes (activating and retrieving stored semantic information) at the expense of integrative processes.

Neuroimaging studies investigating how healthy participants can understand the meaning of words and sentences have recently shown an early motor activation for action verb processing, which has been associated with the retrieval of semantic information (Pulvermuller, Shtyrov, & Ilmoniemi, 2005; van Elk, van Schie, Zwaan, & Bekkering, 2010; Willems, Labruna, D'Esposito, Ivry, & Casasanto, 2011). This early motor activation would reflect a very basic level of language processing and is in accordance with the embodiment theory (for reviews see, for example, Fischer & Zwaan, 2008; Glenberg & Gallese, 2011; Jirak, Menz, Buccino, Borghi, & Binkofski, 2010). The basic concept underpinning this hypothesis is that the neural structures presiding over action execution, by means of reuse, should also play an elementary role in understanding the semantic content of the same actions when verbally described (Gallese, 2008; see also Anderson, 2010). Action simulation has been proposed to reflect an elementary processing level in a more complex neuronal circuit that reciprocally connects actions and perceptual systems (Pulvermuller & Fadiga, 2010; Willems, Hagoort, & Casasanto, 2010).

However, despite increasing empirical support for the contribution of motor representations to the processing of action-related language in healthy individuals, no studies directly investigated motor simulation abilities underlying semantic processing in schizophrenia. Outside the language domain, impaired simulation abilities have been explored by different studies (Bruzzo, Gesierich, & Wohlschlager, 2008; Daprati et al., 1997; de Vignemont et al., 2006; Maruff, Wilson, & Currie, 2003), mostly aimed at testing a deficient self-monitoring system in schizophrenia (e.g., in relation to pathological aspects of self-agency). Accordingly, Park and colleagues (Park, Matthews, & Gibson, 2008) demonstrated reduced imitation skills in schizophrenic patients and hypothesized that deficits in mental simulation could lead to misunderstand others' actions. Although there is general consensus about impaired simulation abilities outside the language domain, the same abilities still remain unexplored in relation to semantic processing deficits in schizophrenia. In particular, it is an open issue at which level in the semantic system these deficits occur and whether they imply impairments at the very basic level of motor representations in schizophrenia, or not. Specifically, it is still unknown whether schizophrenic patients use mental simulation as a basic strategy to understand the meaning of action verbs. Alternatively, motor representations activated during the understanding of action verbs might be intact in patients, and semantic impairments in schizophrenia may depend on alterations at the level of hierarchically higher cerebral structures. In the latter case, alterations in cortical structures concerning the cognitive control of action representation (Badre, 2008; Buccino et al., 2004; Vogt et al., 2007) and language processing (Kuperberg, West, Lakshmanan, & Goff, 2008) may be involved.

To investigate this issue we performed two separate studies. First, by means of a behavioral study we assessed whether First Episode Schizophrenia (FES) patients, like healthy control (HC) participants, use motor simulation as a basic strategy when processing action verbs. In other words, we tested whether patients also perform an internal simulation of the content expressed in action verbs, likely mediated by the activation of the same motor representations that are involved in the execution of the same actions (Buccino et al., 2005). Furthermore, the relationship was investigated between behavioral alterations and schizophrenic symptomatology, in particular basic symptoms, representing subclinical symptoms that appear earlier and remain stable in the disease progression, including the prodromal phase of schizophrenia (Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001; F. Schultze-Lutter, 2009). Second, in order to investigate whether and how brain anatomical alterations would be responsible for the group differences in task performance detected by this behavioral study, a structural MRI of the same participants was acquired to perform a volumetric analysis on gray matter volume.

2. Participants

Nineteen outpatients with FES and 19 matched HC participants were included in the present study (for demographic variables and participant characteristics, see Table 1). All participating FES patients had a history of a single psychotic episode and all received a diagnosis of schizophrenia according to DSM-IV criteria 6 months after the episode. FES patients were recruited from regional mental health centres. All patients responded well to pharmacological therapy indicated by relatively compensated positive and negative symptoms (see Table 1), and stabilized global functioning in daily living. IQ scores showed that the patient group was in the range of the average healthy population with respect to intellectual capacities (mean = 100.6 ± 8.5). However, the mean IQ score was slightly lower for FES (100.8 ± 8.2) patients than for HC (121 ± 10.8). All participants were free of physical health problems and neurological signs. Exclusion criteria included standard contraindications for MRI, a history of severe head trauma, loss of consciousness, drug abuse, IQ < 85, and, for the HC group, a personal history of Axis I/II disorders or a history of psychosis in first-degree relatives.

The study was approved by the local Ethics Committee. Written informed consent was obtained from all participants after full explanation of the procedure of the study, in line with the Declaration of Helsinki. The participants were given a recompense for participating in the experiment.

2.1. Evaluation scales

FES patients were evaluated by the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Williams, & Gibbon, 1996), rated for symptom severity with the Positive And Negative Symptom Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and for intelligence quotient (IQ) by means of the Wechsler Adult Intelligence Scale - Revised (WAIS-R; Wechsler, 1997) by trained psychiatrists. HC participants were evaluated by means of the Structured Clinical Interview for DSM-IV for Axis II personality Disorders (First, Gibbon, & Spitzer, 1996).

Table 1
Demographic information about First Episode Schizophrenia (FES) patients and healthy controls (HC).

	FES patients (*N* = 19)	HC (*N* = 19)
Age (mean ± SD)	27.2 ± 5.4	28.7 ± 5
Months from psychotic episode (mean ± SD)	7.6 ± 5	n.a.
IQ (mean ± SD)	100.8 ± 8.2	121 ± 10.8
Handedness score (mean ± SD)	62.8 ± 20.4	66.9 ± 14.3
Male/female	14/5	11/8
Diagnosis	First Episode Schizophrenia	n.a.
SCID-II Cluster A	n.a.	Negative
SCID-II Cluster B	n.a.	Negative
SCID-II Cluster C	n.a.	Negative
PANSS Positive scale individual scores (mean ± SD)	9 14 17 16 21 14 18 12 10 17 12 13 11 19 13 8 9 11 15 (13.6 ± 3.6)	n.a.
PANSS Negative scale individual scores (mean ± SD)	10 9 10 11 12 16 12 8 10 15 9 13 9 11 22 9 9 12 22 (12 ± 4)	n.a.
PANSS General Psychopathology scale (mean ± SD)	20 30 18 24 32 25 22 22 20 26 20 24 21 25 25 19 20 22 35 (23.7 ± 4.5)	n.a.
SPI-A total score (mean ± SD)	74 91 115 71 67 5 40 36 97 17 12 27 22 83 82 45 49 111 99 (60.15 ± 34.8)	n.a.
Medication	4 Quetiapine 5 Risperidone 4 Paliperidone 3 Aripiprazole 3 Olanzapine[a]	n.a.

[a]Clorpromazine equivalent mean dose 455 mg/die SD = 416 (calculated on 15 patients because no equivalents are available for paliperidone).

2.2. Evaluation scales used for correlation analysis

FES patients were evaluated for the presence of basic symptoms (BS; Klosterkötter et al., 2001) by means of the Schizophrenia Proneness Instrument (SPI-A; Schultze-Lutter, Addington, Ruhrmann, & Klosterkotter, 2007). Basic symptoms define a set of mild self-experienced subclinical disturbances, involving different areas of psychic functioning. They are assumed to play a central role in behavioral disorders and disabilities of psychotic patients, being present in the prodromal phase, in frank psychosis and also after the remission. The basic symptoms therefore represent a nuclear phenomenon in emerging and manifesting psychosis.

3. Study 1: Behavioral

Sato and colleagues (Sato, Mengarelli, Riggio, Gallese, & Buccino, 2008) demonstrated in healthy participants that during action verbs processing the modulation of the motor system crucially occurs while performing a semantic, but not a lexical, decision task. Only in the former case, the authors observed an interference effect for hand action-related verbs, most likely due to the simultaneous involvement of the hand motor system in both understanding the language material and executing the required response. As a consequence, a competition for common motor resources between hand motor response and simulation would occur (see also Buccino et al., 2005). Such interference effect was observed only when participants had to respond after 150 ms from the word presentation, but not when they had to respond after a further 1 s delay. According to the authors, the absence of the interference effect in the delayed condition suggests that the involvement of the motor system is not an accompanying phenomenon of the language task, but that the interference effect is time-locked to the process of verb understanding.

To the aim of understanding whether FES patients, like healthy participants, use motor simulation as a basic strategy when processing action verbs, an adapted version of the go-no go paradigm used by Sato and colleagues (Sato et al., 2008) was used both for the semantic and the lexical task.

3.1. Stimuli

For the *Semantic decision task* thirty Italian verbs were selected as stimuli (for the linguistic material, see Sato and colleagues (Sato et al., 2008; Appendix): 10 verbs expressed a hand-related action (e.g., ‘applaudire’, ‘to applaud’), 10 verbs a foot-related action (e.g., ‘marciare’, ‘to walk’) and 10 verbs had an abstract content (e.g., ‘amare’, ‘to love’). All verbs were presented in the infinitive form and could be three or four syllables long. Verbs in the three categories were matched for syllable number (average values: 3.5, 3.7 and 3.5 syllables for hand-related, foot-related and abstract verbs, respectively) and for word-length (average values: 8.5, 8.8 and 7.7 letters for hand-related, foot-related and abstract verbs, respectively). Mean lexical frequency for hand, foot and abstract-related verbs was 3.03, 8.42 and 9.64 (in occurrences per million), respectively (Laudanna, Thornton, Brown, Burani, & Marconi, 1995). A one-way analysis of variance with three levels, one for each verb category, showed no reliable differences ($F_{(2, 27)} = 1.06$, $p = 0.35$).

For the *Lexical decision task*, 20 verbs and 20 nonsense words were selected. Ten verbs expressed a hand-related action and 10 verbs a foot-related action. The verbs were identical to those used in the Semantic decision task. Nonsense words were built by replacing one consonant into the first or the second syllable of each verb (e.g., ‘firtare’ instead of ‘firmare’). With this procedure, verbs and nonsense words were matched for syllable number (average values: 3.5, 3.7 and 3.6 syllables for hand-related verbs, foot-related verbs and nonsense words, respectively) and for word-length (average values: 8.5, 8.8 and 8.7 letters for hand-related verbs, foot-related verbs and nonsense words, respectively). In no case nonsense words contained orthographically or phonologically illegal bigrams for the Italian language.

3.2. Procedure

The experiments were carried out in a sound-attenuated room. Participants sat comfortably in front of a computer screen at a distance of about 60 cm from it, with the right hand placed over a response pad, positioned in correspondence with the midline of the computer screen.

For the *Semantic decision task*, participants were instructed to carefully read verbs and to give a motor response, as fast and accurately as possible by pressing with the right index finger a button of the response pad when the verb expressed a concrete action, and refrain from responding when the verb expressed an abstract content (go-no go paradigm). Visual stimuli were presented at the center of the computer screen and written in white lowercase Arial font on a black background.

During the experiment, each verb belonging to the three categories was presented four times. Thus, the experiment consisted of 120 trials, run in a single session. Stimuli were randomized for each subject. Each trial started with a red circle presented at the center of the screen. After a variable delay of 150–500 ms (in order to avoid a response habituation), a verb was visually presented. The color change of the circle was the 'go' signal for the response when the verb expressed a hand or foot action-related verb. The Go-signal for the response was delivered at two distinct time points from the verb presentation. It appeared, in half of the trials, at 150 ms after the verb presentation (Early Go-signal Delivery, EGD), and, in the other half of the trials, at 950–1150 ms (Delayed Go-signal Delivery, DGD). A period of 150 ms from the onset of verb presentation has been shown to be sufficient to recruit frontal areas during reading (Hauk & Pulvermuller, 2004). The intertrial interval was 3000 ms. During this interval the PC screen remained blank. During the experiment, each verb of the three categories was presented twice for each time point at which the go signal was given (normal and 800–1000 ms delayed).

For the *Lexical decision task* participants were instructed to give a response when the stimulus was a word and refrain from responding when the stimulus was a nonsense word. As in the previous experiment participants gave their responses using their right index. The stimuli were presented only with the Go-signal delivered 150 ms after the onset of the verb presentation (EGD). During the experiment, each stimulus was presented twice. Thus, overall 80 trials were given in a single session. Verbs sequences were randomized for each subject. We used the Lexical decision task as a control task to make sure that differences between hand-related verb processing and foot-related verb processing were specifically due to the use of a motor simulation strategy. Indeed, this strategy is required in the Semantic, but not in the Lexical decision task.

Half of the participants performed firstly the Semantic task, and the other half started with the Lexical decision task, according to a pseudorandomized attribution of the participants to one of the conditions.

3.3. Data analysis

3.3.1. Inverse efficiency

Trials in which reaction-times (RTs) from the go-signal were faster than 130 ms were considered as errors (i.e., anticipations) and discarded without replacement.

In order to provide a measure of overall performance that simultaneously takes into account speed and accuracy, we used the method first recommended by Townsend and Ashby (Townsend & Ashby, 1983) that has subsequently been referred to as "inverse efficiency" (IE; Christie & Klein, 1995). For each participant of both groups, IE scores were calculated, for each verb category (Hand or Foot action) and time of the Go-signal delivery (EGD or DGD). To this aim, the median values for correct RTs were divided by their corresponding proportion correct score so that differences in RTs performance decreased if differences in accuracy were large but remained the same if accuracy was identical. Thus, IE scores provided a measure of overall performance. Lower IE corresponded to better performance. These IE scores were then entered an analysis of variance (ANOVA) for each task. Whenever appropriate, post hoc analyses were performed with the Newman–Keuls method. Unless differently indicated, an alpha level of 0.05 was used.

In the Semantic decision task, Verb category (Hand or Foot action) and Time of the Go-signal delivery (EGD or DGD) were treated as within-subjects variables and Group (Controls or Patients) as a between-subjects variable.

In the Lexical decision task, an ANOVA was carried out with Verb category (Hand or Foot action) as a within-subjects variable and Group (Controls or Patients) as a between-subjects variable.

3.3.2. Effect of motor simulation on discriminability of go trials from no-go trials

Differences between HC and FES in the use of motor simulation strategy may have an effect on their ability to the discriminate go trials from no-go trials during task performance, that is, sensitivity. We tested this hypothesis by applying the signal detection theory model (Green & Swets, 1966). Hit rate (H, probability of response inhibition on no-go trials) and false alarm rate (FA, probability of response inhibition on go trials) were established to determine d' (sensitivity) in each group and for each time of the Go-signal delivery (EGD or DGD). Hit and false alarm rates were referred to standardized normal distributions in order to yield z(H) and z(FA). The sensitivity index d' is given by z(H)-z(FA) expressed in normal deviates. Independent samples T-tests were computed to compare HR, FA and d' between FES and HC.

3.3.3. Correlations between action-verb simulation and symptomatology

The relationship between symptomatology assessed by the Schizophrenia Proneness Instrument Adult Version (SPI-A, Schultze-Lutter et al., 2007) and patients' propensity to simulate action-related verbs during the Semantic decision task was examined using the Spearman coefficient (ρ).

As the variable indicating the propensity to simulate the content of action-related verbs, we used the difference between IE scores for Hand (H) and Foot (F) action related verbs, for both the Early Go-signal delivery condition (HE and FE) and the Delayed Go-signal delivery condition (HD and FD). The higher the difference [IE(HE-FE)] and [IE(HD-FD)], the stronger the propensity to simulation.

3.4. Results

3.4.1. Inverse efficiency scores

Semantic decision task. IE scores were calculated from accuracy and reaction time values reported in Table 2. An ANOVA was performed with IE scores as dependent variable, Group (controls vs. patients) as a between-subjects factor, and Time of the Go-Signal Delivery (Early, Delayed) and Verb Category (Hand, Foot) as within-subjects factors. ANOVA results are shown in Fig. 1. ANOVA revealed a main effect of Group ($F_{1,36} = 8.9$, $p < 0.01$), with worse

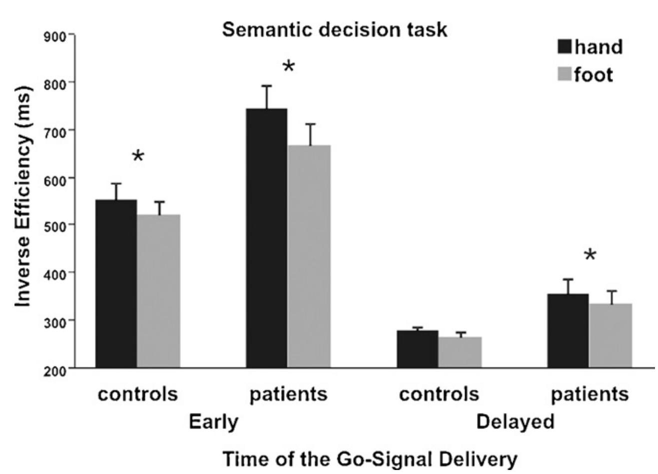

Fig. 1. Participants' adjusted reaction times (i.e., inverse efficiency scores) to stimuli presented in the semantic decision task (Study 1). Go signal was delivered after 150 ms (early delivery) and after 950–1150 ms (delayed delivery). Bars represent standard errors. $^{*}p \leq 0.05$.

Table 2
Reaction time (RT) scores (ms; prior to adjustment for inverse efficiency) and accuracy (%) in each subject group (healthy control group, HC, and first episode schizophrenia group, FES.

	Semantic decision task				Lexical decision task			
	RT		Accuracy		RT		Accuracy	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
HC								
HE	556	25.5	0.98	0.02	493	21.5	0.97	0.01
FE	527	23.9	0.99	0.01	486	20.4	0.97	0.02
HD	275	8.3	0.95	0.02	–	–	–	–
FD	268	8.8	0.97	0.01	–	–	–	–
FES								
HE	721	45.6	0.94	0.02	660	56.6	0.94	0.02
FE	681	41.6	0.98	0.01	666	52.4	0.95	0.02
HD	344	29.4	0.91	0.02	–	–	–	–
FD	328	23.5	0.92	0.02	–	–	–	–

HE: Hand verbs, Early go-signal delivery; FE: Foot verbs, Early go-signal delivery; HD: Hand verbs, Delayed go-signal delivery; FD: Foot verbs, Delayed go-signal delivery).

performance for patients (527 ms) than controls (407 ms), and a main effect of Time of the Go-Signal Delivery ($F_{1,36}$ = 23.4, $p < 0.001$), with both groups performing worse for the Early (624 ms) than for the Delayed (310 ms) delivery of the Go-signal. Also the main effect of the Verb Category was significant ($F_{1,36}$ = 23.4, $p < 0.001$). Both patients and controls performed worse with Hand action verbs (485 ms) than Foot action verbs (449 ms). These effects were qualified by a significant interaction between Group and Time of the Go-signal Delivery ($F_{1,36}$ = 6.6, $p < 0.05$). Post hoc comparisons showed that performance was worse for patients than controls for the EGD (707 ms vs. 540 ms, $p < 0.01$), but not for the DGD (347 ms vs 273 ms, $p = 0.21$), condition. Furthermore, the interaction Time of the Go-signal Delivery × Verb Category was also significant ($F_{1,36}$ = 14.3, $p < 0.001$). Post hoc analysis showed that all the pair-wise comparison were significant ($p < 0.05$, in all cases).

Interestingly, the 3-way interaction Group × Time of the Go-signal Delivery × Verb Category approached statistical significance ($F_{1,36}$ = 3.7, $p = 0.06$). Post hoc analysis showed that for EGD condition both patients and controls performed worse with Hand action than Foot action verbs (746 ms vs. 668 ms and 556 ms vs. 524 ms, $p < 0.005$ for all comparisons). Instead, for the DGD condition only patients showed such a different performance for Hand action compared to Foot action verbs (patients: 357 ms vs. 337 ms, $p = 0.05$; controls: 280 ms vs. 267 ms, $p = 0.21$).

Lexical decision task. IE scores were calculated from accuracy and reaction time values reported in Table 2. An ANOVA was performed with Group (controls vs. patients) as a between-subjects factor, and Verb Category (Hand, Foot) as a within-subjects factor. Data are shown in Fig. 2. This analysis showed only a main effect of Group ($F_{1,36}$ = 5.5, $p < 0.05$), with patients having higher IE scores than controls (689 ms vs. 501 ms). What is important to note here is that also FES participants, just as controls, performed equally with Hand action and Foot action verbs.

3.4.2. Different discriminabilty of go trials from no-go trials in the Delayed go-signal delivery condition

IE analysis concerning the semantic decision task showed that differences between Hand action and Foot action verbs during the EGD condition were similar for both groups ($p < 0.005$ for all comparisons). Interestingly, during the DGD condition a similar difference was observed only for the patients ($p = 0.05$) and not for the healthy controls ($p = 0.21$). This seems to have an effect on groups' ability to the discriminate go trials from no-go trials in the same condition. Indeed, independent samples *t*-test revealed significant differences for d' among the two groups in DGD condition (T_{36} = 2.28, $p < 0.05$), but not in EGD condition (T_{36} = 0.96, $p = 0.34$). Mean values for Hit rate, False alarms and d' of each subject group

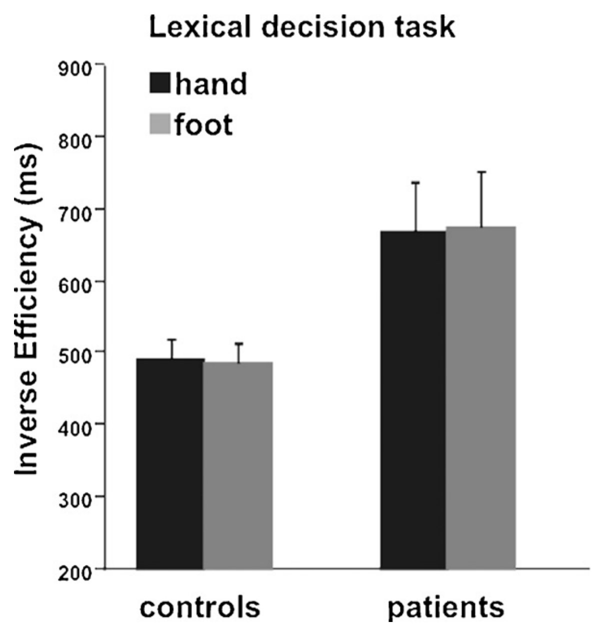

Fig. 2. Participants' adjusted reaction times (i.e., inverse efficiency scores) to stimuli presented in the lexical decision task (Study 1). Go signal was delivered after 150 ms (early delivery). Bars represent standard errors.

(HC and FES) and for each condition (DGD and EGD) are reported in Table 3.

3.4.3. Correlations between behavioral results and symptomatology

We assessed the relation between measures of specific symptomatology and patients' propensity to simulate the content of words. SPI-A total score correlated negatively with [IE(HD-FD)], ($\rho = -0.55$, $p = 0.01$), but not with [IE(HE-FE)], ($\rho = -0.35$, $p = 0.15$; Fig. 3).

Table 3
Mean (SE) values for Hit rate, False alarms and d' of each subject group (healthy control group, HC, and first episode schizophrenia group, FES) in the Semantic decision task.

	DGD condition		EGD condition	
	HC	FES	HC	FES
Hit rate (%)	0.96 (0.01)	0.91 (0.01)	0.98 (0.01)	0.96 (0.01)
False alarms (%)	0.02 (0.01)	0.02 (0.01)	0.06 (0.02)	0.08 (0.02)
Sensitivity (d')	4.9 (0.23)	4.2 (0.23)	4.4 (0.22)	4.0 (0.33)

DGD: Delayed Go-signal delivery; EGD: Early Go-signal delivery.

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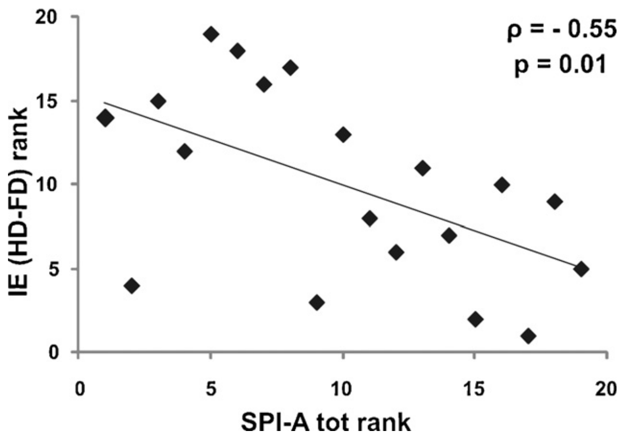

Fig. 3. Correlation (ρ) between patients' propensity to motor simulation (i.e., differences between IE scores for Hand (H) and Foot (F) action verbs computed for each participant) and symptomatology assessed by the Schizophrenia Proneness Instrument Adult Version (SPI-A; i.e., basic symptoms).

3.5. Discussion (Study 1)

The first study aimed at investigating whether semantic impairments in schizophrenia can be explained by deficits at a very basic level of language processing, such as motor representations underlying semantic retrieval. We attempted to answer the specific question of whether in FES the semantic understanding of action verbs relies on the same strategies as in healthy controls, that is, motor simulation. For this purpose, we used the same experimental go-no go paradigms as Sato and colleagues (2008) comprising a semantic decision task with either an early or a delayed delivery of the go-signal (during processing language material) as well as a lexical decision task with an early delivery of the go-signal.

Differences in task performance were found between the HC and FES group. The IE analysis showed that patients generally performed worse than controls, both in the semantic and in the lexical decision task. Specifically for the semantic decision task, both patients and controls performed worse with Hand action than Foot action verbs, in the EGD condition. Such results confirmed the interference effect reported by Sato and colleagues (2008), likely reflecting the simultaneous activation of multiple motor representations. Relevantly, this interference effect could also be detected in FES patients. Although task performance of the FES group appeared less efficient than in the control group, this suggests that FES patients used the same motor strategy as healthy controls, while performing the semantic task. Given that the reduced efficiency detected in FES patients could be observed in all the experimental conditions, including the lexical task, it seems unlikely that this can be related to a deficit in action simulation underlying action verb processing.

Previous studies (Bruzzo et al., 2008; Daprati et al., 1997; Franck et al., 2001; Maruff et al., 2003) suggested motor simulation deficits in schizophrenia. It should be noted that they mostly aimed at testing the self-monitoring system in schizophrenic patients. In contrast, our results suggest that the simulation ability is not impaired when applied to the processing of action-related language, at least in FES patients.

Another result of particular interest is that FES patients, differently from HC, showed an interference effect for hand verbs (i.e., worse performance with Hand action verbs than Foot action verbs) also for the DGD condition. Although this result needs to be interpreted with caution, considering that the 3-way interaction Group × Time of the Go-signal Delivery × Verb Category Effector only approached statistical significance ($p = 0.06$), it suggests that FES patients keep on using the simulation strategy also in the DGD condition. Such a prolonged activation of a motor representation might be related to an impaired selection (not proceeding to next level and not attenuating activation; e.g., see Badre, 2008) due to a dysfunction of hierarchically higher order processes, involved in the cognitive top-down control of action representations (Badre, 2008; Buccino et al., 2004; Vogt et al., 2007). In other words, it could reflect an impairment in the regulation of the motor simulation strategy for action verb processing in FES.

An alternative explanation for the interference effect for Hand action verbs for the DGD condition in FES patients is that they might have adopted a prolonged motor simulation in the delayed condition (i.e., an effector-specific simulation of word content) as a compensatory strategy. Supporting this hypothesis there is the negative correlation between total basic symptom score and the IE scores for hand action-related verbs, only for the delayed but not for the early go-signal delivery conditions. In other words, this interpretation suggests that FES patients with more severe symptomatology show a stronger compensation strategy reflected by a stronger interference effect. It could be argued that prolonged motor simulation is used to compensate for higher level memory deficits by keeping active the motor program representing the verb's meaning during the delay and, hence, facilitating memory.

However, we also found that differences between HC and FES participants in the use of motor simulation strategy were accompanied by reduced abilities to discriminate go-trials from no go-trials and to inhibit response on no-go trials during task performance. Sensitivity (d') and hit rate indices significantly differed between the two groups specifically for the DGD condition, suggesting in FES a reduced ability to discriminate between abstract and concrete action verbs. Two possible explanations can be proposed for impaired discrimination for the DGD conditions. On the one hand, the prolonged motor simulation could have interfered with task performance. On the other hand, motor simulation might not fully compensate for other deficits (e.g., working memory). Since the lexical task did not include a DGD condition, we are not able to distinguish between those alternatives. One could speculate that in the first case the ability to discriminate between go and no go trials would have been intact, whereas in the second case it would have been impaired.

4. Study 2: Voxel-based morphometry

The results from Study 1 suggest that FES patients have intact simulation abilities underlying the processing of action verbs meaning. Nevertheless, altered performance in FES patients for the DGD condition show that they relied on a different use of this kind of strategy when compared with controls. This is reflected by a reduced ability to discriminate between go and no-go trials, that is, a reduced discriminability between abstract and concrete action verbs. Therefore, it is possible that a deficit in semantic processing in FES patients is not related to motor regions underpinning motor simulation, but rather to other brain regions associated with a different level of action verb processing.

In accordance with models of hierarchical control of cognitive functions and with the role of DLPFC in the selection of an appropriate action representation (Badre, 2008; Koechlin, Ody, & Kouneiher, 2003), the observed alterations in task performance could be due to impaired selection function by superior control areas (not proceeding to next level and not attenuating activation). Alternatively, FES patients might have adopted a motor simulation strategy in the delayed condition (i.e., an effector-specific simulation of word content) as a compensatory strategy.

Previous studies demonstrated that gray matter volumetric alterations in schizophrenic patients are localized in mid-rostral middle frontal gyrus (Kikinis et al., 2010), and that a functional

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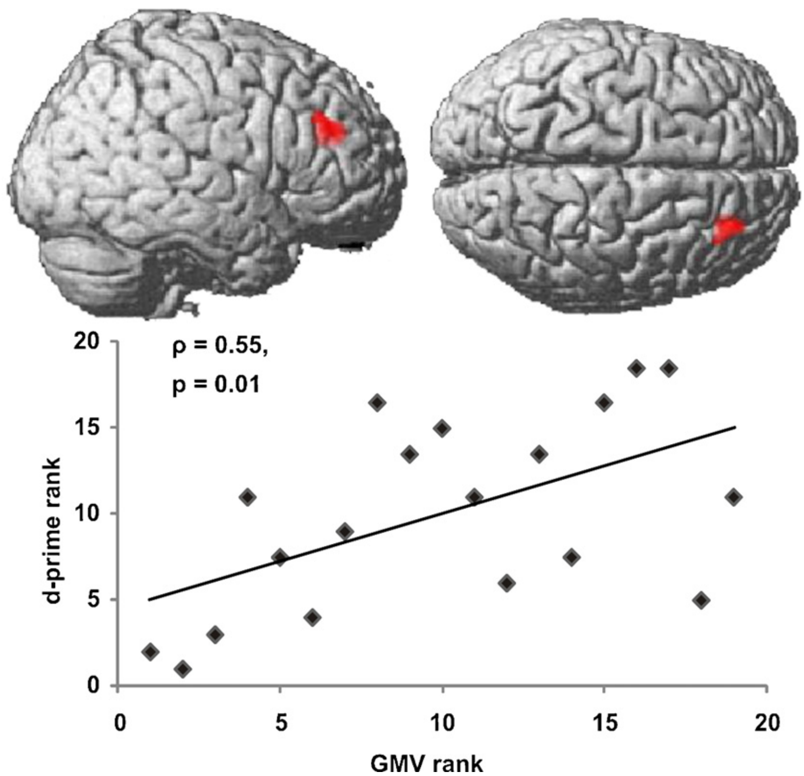

Fig. 4. Correlation (ρ; visualized in bottom panel) between regional gray matter (GM) within the DLPFC (BA 46; peak MNI coordinates at 28, 36, 25; visualized in upper panel) and patients' ability to distinguish between abstract and concrete words (estimated by computing d' values).

deficit of higher-order processing regions, such as the right dorsal prefrontal cortex (Brodmann's Area 46) can result in compensatory brain activity supporting compensatory strategy. For example, Tan et al. (2006) suggested that the altered functional organization of the dorsal prefrontal cortex in schizophrenic patients could result in a compensatory activation of the ventral prefrontal areas hypothesized to be involved in action verb understanding (especially Brodmann's Area 44). In addition, Kuperberg and colleagues (2008) showed that dysfunction during the construction of higher-order meaning in schizophrenia was due to the fact that patients failed to recruit the DLPFC. As suggested by the authors, patients rely relatively more on semantic retrieval of stored information (dependent on inferior frontal and temporal processes) at the expense of integrative processes (additionally recruiting DLPFC).

Based on this kind of knowledge, we hypothesized that gray matter volumetric alterations in FES patients' DLPFC could be related to between-group differences in task performance for the DGD condition.

4.1. MRI acquisition

A high-resolution structural volume was acquired via a 3D MPRAGE sequence with the following features: 170 sagittal slices, voxel size: 1.25 mm × 1.25 mm × 1.20 mm, TR = 8.6 ms, TE = 4.0 ms, 192 × 192 image matrix, FOV = 240 mm. Images were collected with a 1.5 T Philips Achieva scanner operating at the Institute of Advanced Biomedical Technologies (I.T.A.B. Fondazione G. d'Annunzio, Chieti, Italy).

4.2. Data analysis

4.2.1. Voxel-based morphometry

Brain structural data were processed and examined using the SPM8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), where we applied *Voxel-based morphometry* (VBM) implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters. Images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and non-linear transformations (warping), within a unified model (Ashburner & Friston, 2005). Subsequently, analyses were performed on gray matter (GM) and white matter (WM) segments, which were multiplied by the non-linear components derived from the normalization matrix in order to preserve actual GM and WM values locally (modulated GM and WM volumes). Importantly, the segments were not multiplied by the linear components of the registration in order to account for individual differences in brain orientation, alignment, and size globally. Finally, the modulated volumes were smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM). Voxel-wise GM and WM differences between patients and controls were examined using independent-sample t-tests. In order to avoid possible edge effects between different tissue types, we excluded all voxels with GM or WM values of less than 0.1 (absolute threshold masking). We applied a threshold of $p < 0.001$ with an extent of 75 voxels across the whole brain. The resulting regions are listed in Table S1.

To avoid false positive results due to multiple testing a small volume correction for multiple comparisons (family wise error, FWE (http://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf page 218); P_{FWE}) on voxel level was applied using a mask of left and right Brodmann Area (BA) 46 as region of interest. Regions of interest were defined by using the Hierarchical Automated Anatomical Labeling (HAAL) running on SPM (Lancaster et al., 1997; Tzourio-Mazoyer et al., 2002).

4.2.2. Correlation between d' and cortical gray matter

Correlation analysis was performed between regional gray matter (estimated as the mean signal extracted from the peak voxel) and patients' ability to distinguish between abstract and concrete words (estimated by computing d' values) using the Spearman coefficient (ρ).

4.3. Results

We found a significant difference between *controls and patients* in terms of GM within the DLPFC (BA 46) (peak MNI coordinates at 28, 36, 25; cluster volume: 893 mm^3; $p < 0.01$ FWE), with reduced volume in the FES group, compared with the HC group. In addition, we found a positive correlation ($\rho = 0.55$, $p = 0.01$) between GM volume in patients' right DLPFC and d' for the DGD condition (Fig. 4).

4.4. Discussion (Study 2)

In order to elucidate the possible brain basis of the behavioral alterations observed in the FES group, we performed a volumetric evaluation of cortical areas. Based on previous studies on schizophrenic patients, both related to their GM volumetric alterations (e.g., Kikinis et al., 2010) and to their dysfunction in the construction of higher-order meaning (e.g., Kuperberg et al., 2008), we focused on GM alterations in the DLPFC.

VBM results showed that FES patients were characterized by significantly smaller GM volumes in DLPFC (BA 46), compared to HC participants. Moreover, we found a positive correlation between patients' regional GM and their sensitivity (d') in discriminating between go trials (concrete words) and no-go (abstract words) trials.

GM volumetric alterations in schizophrenic patients in the right DLPFC (BA46) have already been described by Kikinis and colleagues (2010). Earlier studies based on models of hierarchical control of cognitive functions suggested a role of DLPFC in the selection of an appropriate action representation (Badre, 2008; Koechlin et al., 2003). Previous fMRI data (Buccino et al., 2004; Vogt et al., 2007) seemed to suggest that the motor representation subserving the perception-action matching, involved in the early stages of imitation learning, is under the supervisory control of the left DLPFC (BA 46). A robust functional coupling between the DLPFC and the two components of the fronto-parietal mirror circuit (FPMC) has been recently found by applying Psycho-Physiological Interactions (Higuchi, Holle, Roberts, Eickhoff, & Vogt, 2012). Using the same experimental paradigm as in Buccino and colleagues' study (2004), Higuchi and colleagues (2012) confirmed that during both imitative execution and learning by observation the DLPFC is exerting a supervisory and monitoring role over the elementary representations provided by the FPMC. In the same vein, right DLPFC has been described as the inhibitory component keeping us from automatically imitating everything we see by influencing motor areas (Bien, Roebroeck, Goebel, & Sack, 2009). Indeed, by means of effective connectivity analysis (Granger Causality Mapping), a flow of information from the right DLPFC to premotor cortex, and from here to parietal cortices, was shown. In the same study (Bien et al., 2009), the comparison between results separately obtained after TMS-induced DLPFC and premotor disruption indicated that whereas premotor cortex is involved in automatic imitation, DLPFC subserves general response inhibition.

Our results suggest that in the domain of language a similar top-down control by prefrontal cortical areas may occur over motor areas implicated in action verb processing. A possible reduced control of DLPFC over hierarchically lower structures, such as premotor areas, would result in persistent use of the simulation strategy, thus reducing the ability to discriminate (d') concrete (go trials) from abstract (no-go trials) words. This hypothesis is also coherent with a role of DLPFC dysfunction in schizophrenia proposed by Kuperberg and colleagues (2008). According to the authors such a dysfunction would result in a deficit in the construction of higher-order meaning.

5. General discussion

We found that FES patients, like HC participants, use motor simulation as a basic strategy to process the meaning of action verbs. Both motor simulation and action verb understanding seem to be preserved in FES, at least for the short time course over which the meaning of the word has to be maintained during the task. However, differently from HC participants, FES patients seem to keep on using the simulation strategy also in the DGD condition. Moreover, task performance during the DGD condition appeared to be less efficient and sensitive than that used by HC participants for the same condition. Anatomically, this altered performance in FES patients could be related to right DLPFC. This link would be coherent with the well-accepted DLPFC dysfunction in schizophrenia.

We propose that a prolonged activation of motor representation could be due to an impaired selection function by superior control areas (not proceeding to next level and not attenuating activation). Alternatively, patients might have adopted a motor simulation strategy to compensate for higher level memory deficits by keeping active the motor program representing the verb's meaning during the delay and, hence, facilitating memory. This hypothesis is in line with previous studies (Chenery, Copland, McGrath, & Savage, 2004) that used semantic priming with short and long stimulus onset asynchrony (SOA). They revealed enhanced remote priming at short SOA, whereas marked anomalies were reported in maintaining semantic information over an extended temporal delay in patients with schizophrenia.

The negative correlation we found between simulation of hand-related verbs and Basic Symptom scores support this proposal of a compensatory strategy, indicating that FES patients with better subjective clinical conditions rely more on the simulation strategy to understand the meaning of action verbs in a DGD condition.

The present study is not able to disentangle this issue, though the two hypotheses above illustrated do not necessarily exclude each other and both theoretically could be related to DLPFC. However, limited to the semantic domain of language investigated in the present study, we propose that a prolonged motor simulation in FES might serve as a compensatory strategy for impairments in the selection of action representation and/or for memory deficits, which can be both related to DLPFC dysfunction.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2012.02.005.

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