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Research report

Implicit olfactory processing attenuates motor disturbances in idiopathic Parkinson's disease

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ABSTRACT

Many reports in the literature indicate that idiopathic Parkinson's disease (IPD) patients have substantial olfactory dysfunctions even before motor symptoms become evident. It has not yet been clarified, however, if some form of implicit olfactory processing is preserved in this population. An olfactory visuomotor priming paradigm, which detects implicit olfactory processing in neurologically healthy participants, was utilized to investigate motor control in relation to olfactory signals in a group of IPD patients. Two control groups were also considered: 12 vascular Parkinson's disease (VPD) in whom normal olfactory abilities are typically reported and 12 neurologically healthy participants. All of the participants were asked to perform reach-to-grasp movements toward large or small targets following olfactory cues delivered by a computer-controlled olfactometer. The odor was either 'size' congruent with the target (e.g., strawberry or apple, respectively) or incongruent (e.g., apple or strawberry, respectively). A bend sensor glove (CyberGlove) was used to measure the hand kinematics. Facilitation effects were noted in all the groups with regard to movement time. If a congruent rather than an incongruent odor was delivered, the movement time of the reach-to-grasp was shortened and facilitation effects in maximum grip amplitude were noted in both the IPD and the VPD groups. The maximum grip amplitude was smaller when no odor, as compared to a congruent odor, was delivered. The present results suggest that implicit olfactory processing affects motor control in IPD patients favoring less severe bradykinesia and hand movement hypometria. Once confirmed, these findings could be useful when rehabilitation strategies are being hypothesized for these patients.

1. Introduction

Parkinson's disease (PD) is principally characterized by motor disturbances which are often the reason these patients seek their physicians' attention. These disturbances reflect, at least in part, a pathological loss of dopaminergic neurons in the ventral midbrain and nerve terminal degeneration in the striatum (Bernheimer et al., 1973). The greater the neuronal

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loss in the substantia nigra, the lower the concentration of dopamine in the striatum, and the more severe symptoms are in these patients. Typically, by the time PD is clinically diagnosed, a significant loss of dopaminergic neurons has already occurred.

Although a progressive loss of nigral neurons is considered an essential neuropathological feature, recent findings in the literature seem to suggest that PD is characterized by a variety of symptoms which go beyond motor disturbances (Braak et al., 2003, 2004; Chaudhuri et al., 2006; Ziemssen and Reichmann, 2007). A great deal of attention has been paid to PD-related non-motor symptoms such as sensory disorders, autonomic dysfunctions, mood and sleep disorders, cognitive deficits and hyposmia which appear to be perceptible even before motor parkinsonism becomes explicit (Braak et al., 2003, 2004; Wolters and Braak, 2006).

Olfactory dysfunction is a non-motor symptom that has long been described in patients with PD (Doty, 2003). A significant decrease in odor detection, discrimination, and identification has, in fact, frequently been reported in PD patients with respect to neurologically healthy controls (Ansari and Johnson, 1975; Korten and Meulstee, 1980; Quinn et al., 1987; Hawkes et al., 1997, 1999; Double et al., 2003).

Structures such as olfactory bulbs, olfactory tracts, and/or the anterior olfactory nuclei appear to be affected early during disease development (Tissingh et al., 2001; Del Tredici et al., 2002; Braak et al., 2003, 2004). Although olfactory deficits could be related to dopaminergic loss, Huisman et al. (2004) used tyrosine hydroxylase immunohistochemistry to show that the number of dopaminergic cells within the olfactory bulbs of PD patients was doubled with respect to that generally found in neurologically healthy subjects. This finding led to the hypothesis that increased levels of dopamine within the olfactory glomeruli might determine an inhibitory transmission in the olfactory bulb. Possibly responsible for this condition in PD, the inhibitory process described might explain why hyposmia in these patients is not levodopa-responsive (Huisman et al., 2004).

Although it is well established that the majority of patients with idiopathic Parkinson's disease (IPD) have a defective sense of smell, a large number of investigations have utilized olfactory tests which require an explicit report of odor features (e.g., Doty et al., 1988; Daum et al., 2000; Haehner et al., 2009). Such explicit report implies specific forms of odor memory involving the generation of a name or the odor identification for the participant to respond (Olsson et al., 2002). This aspect is particularly relevant in PD, given that studies addressing odor recognition memory performance seem to suggest that such function in PD patients is impaired (Corwin et al., 1985; Zucco et al., 1991; Kesslak et al., 1988; Mesholam et al., 1998). At a neural level, this finding seems to be supported by studies reporting that olfactory perception may preferentially recruit the hippocampus, possibly reflecting its role in the working memory element of odor-related tasks (Kareken et al., 2003; Bohnen et al., 2008a, 2008b).

In everyday life, nevertheless, odors are rarely encountered in isolation and generally exist in a contextual relationship with other details. In most cases odors are learned unintentionally and unconsciously (Issanchou et al., 2002; Wilson and Stevenson, 2006). As a result, it is difficult to describe odors in terms of specific constituents, and attention is generally focused on individuals' reactions to odor-related events rather than on the identity or the names of odors per se (Engen, 1987; de Wijk and Cain, 1994). Not surprisingly, while people seem to have more difficulty in naming objects via smell than via sight (Cain et al., 1995), they nevertheless negotiate the world of odors quite successfully. While means of encoding odors other than language seem to be utilized, both explicit and implicit processing could be involved in forging the rather complex relationship between odors, their sources, and behaviors connected to them.

Until now, no studies have attempted to assess if any kind of implicit odor processing occurs in PD patients, but recent findings concerning the role played by olfactory stimuli in shaping motor behavior can provide some insight into the direction research should take (Castiello et al., 2006; Tubaldi et al., 2008a, 2008b). Experiments were devised by some investigators to study reach-to-grasp movements performed in the presence or absence of an orthonasal olfactory task-irrelevant stimulus. In some of the experiments the olfactory stimulus evoked an object that was smaller or larger than the visual target utilized. The maximum distance between the index finger and the thumb (i.e., maximum grip amplitude) was found to be affected in different ways depending on the stimulus. If the olfactory stimulus evoked an object that was smaller than the visual target, the maximum grip amplitude was smaller than the one associated to a no-odor clue, but if it evoked an object that was larger than the visual target utilized, the maximum grip amplitude was larger than that associated to a no-odor clue. Moreover, when the 'size' of the odor stimulus and the size of the visual target corresponded, facilitation effects were noted: movement time was, in fact, shorter compared to situations in which the visual target did not correspond to the olfactory stimulus or when there was no olfactory clue. Taken together, these findings seem to indicate that although an olfactory stimulus is irrelevant as far as task performance is concerned, it is nevertheless implicitly elaborated in motor terms to facilitate – or interfere with – the motor plan prepared for the visual target.

Based on the hypothesis that if some sort of implicit olfactory processing still takes place in PD patients this would be reflected in their motor behavior, we designed a reach-to-grasp experiment (e.g., Müller and Stelmach, 1992; Castiello et al., 1993; Saling et al., 1996; Gordon et al., 1997; Tresilian et al., 1997; Gordon, 1998) and added an olfactory stimulus. This population has commonly been found to be slower and to reach smaller peak amplitudes than age-matched control participants but, in other respects, task performance appears to be similar in the two groups. At the same time, studies concerning the influence of olfactory stimuli on reach-to-grasp movements in neurologically healthy individuals have reported alterations in the same specific movement's parameters found in the PD patients (Castiello et al., 2006; Tubaldi et al., 2008a, 2008b).

IPD patients were thus asked to carry out reach-to-grasp movements in the direction of visual targets of different sizes in the absence or presence of preliminary olfactory stimuli that were size congruent or incongruent with the visual targets. The performance of these patients was compared with that in VPD patients with no specific olfactory

deficits but demonstrating similar motor symptoms. A group of neurologically healthy participants was also assessed for comparison purposes.

Basing our premise on already published findings on olfactory stimuli and reach-to-grasp movements, we hypothesized that if implicit olfactory processing is preserved in IPD, the size information conveyed by an odor stimulus would affect the reach-to-grasp movements in different ways depending on the congruency between the motor plans elicited by the odor 'size' and the sight of the visual target. We expected to see that in incongruent situations the motor plan elicited by the visual target would interfere with that elicited by the olfactory stimulus. In congruent conditions in which both the olfactory and visual information elicit a similar motor plan, we expected to see facilitation effects reflected in the degree of bradykinesia and hand movement hypometria in both IPD and VPD patients. Finally, for the neurologically healthy group, we expected to see a similar odor facilitation/interference pattern noted in the two PD groups, but only with regard to movement time.

2. Methods

2.1. *Participants*

Three groups of participants were recruited for the study. Those in the first group ($N = 12$; mean age 67.75 years, average disease duration 2.33 years, mean age at onset 65.42 years) were all diagnosed with IPD and being treated with dopaminergic drugs known to have little or no effect on olfaction (Doty et al., 1992; Neundörfer and Valdivieso, 1977, Table 1). Patients with vascular lesions detected on magnetic resonance imaging (MRI) were excluded from the study with the exception of those with minimal evidence of small vessel disease considered normal for the patient's age and in areas other than the basal ganglia (Katzenschlager et al., 2009). Evaluation of the scans was made by an independent radiologist who was blinded to the study design and modality. The second group ($N = 12$; mean age 68.58 years) was composed of age- and sex-matched VPD patients. Demographic information, clinical data, vascular risk factors (Winikates and Jankovic, 1999) and imaging details for these patients are outlined in Table 2. The severity of PD symptoms in the patients studied was assessed by a board certified neurologist using two different measures: the Hoehn and Yahr (1967) severity scale and the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton, 1987). All of the IPD and three of the VPD patients were tested after they had taken their medication. The fact that levodopa was producing optimal therapeutic responses was provided by the UPDRS which was administered to those patients prior to their respective experimental session. None of the participants showed therapy-related motor complications that could interfere with the study task. A third group ($N = 12$; mean age 65.83 years) was made up of normal participants without neurological or skeletomotor dysfunctions. The Mini-Mental State Examination (MMSE) was used to provide an index of the patients' current global cognitive state (Folstein et al., 1975). The scores of the IPD and VPD patients ranged between 29 and 30 (Tables 1 and 2) while all the neurologically healthy participants had a score of 30. Mean age was not significantly different in the groups studied nor were there significant differences in terms of disease duration in the two patient groups. Both the IPD and VPD patients scored an average of 18 out of 20 on the visual acuity test, while the neurologically healthy participants scored 20 out of 20. All the patients and the controls were non-smokers. Patients with a history of nasal or sinus surgery, severe head trauma, obstructive pulmonary disease, or allergies causing nasal congestion were excluded from the study. Olfactory function was tested using the University of Pennsylvania Smell Identification Test (UPSIT, Sensonics, Haddon Heights, New Jersey, USA) consisting of 40 odors, which are microencapsulated in paper strips and released when they are scratched with a pencil. Participants are asked which of four words best

Table 1 – Demographic data and clinical features of the IPD patients studied.

PD patient	Age (years)	Sex	Years since diagnosis	Stage of the disease	Most affected upper limb	UPDRS (upper limb)	UPSIT score	MMSE score	Dopaminergic medication	Clinical signs						
										T	R	B	A	P	O	F
1	66	M	3	II	L	2	17	28	0–0–0	–	–	+	+	–	–	–
2	68	F	2	II	R	8	14	30	1–1–1*	–	–	+	+	–	–	–
3	71	F	1	I	R	6	14	30	0–0–0	–	+	R	–	–	–	–
4	67	M	2	II	L	5	17	30	1–0–1*	–	+	+	+	–	–	–
5	68	M	2	I	L	3	15	30	1–1–1*	R	+	+	+	–	–	–
6	66	M	3	II	L	10	17	29	1–1–1*	–	+	R	+	–	–	–
7	65	F	4	II	L	4	18	30	0–0–0	–	+	+	–	–	–	–
8	69	M	2	I	R	8	12	30	0–0–0	–	–	+	–	–	–	–
9	68	F	3	I	R	5	15	29	0–0–0	–	–	R	L	–	–	–
10	66	F	1	II	L	9	15	30	.5–.5–.5†	–	–	+	+	–	–	–
11	71	F	2	II	L	12	13	30	1–1–1	R	R	+	+	–	–	–
12	68	M	3	I	L	2	17	30	0–0–0	–	–	R	–	–	–	–

Medication: number of tablets morning–midday–evening (dopaminergic medication, *50 mg; †125 mg). Clinical signs: signs when medicated, according to examination at time of testing and self report: T = resting and/or postural tremor, R = rigidity, B = bradykinesia, A = akinesia, P = problems with static and dynamic upright posture, O = on–off phenomenon, F = freezing; '+' = both sides affected; '–' = neither side noticeably affected; 'L' = left side mainly affected; 'R' = right side mainly affected. Stage of the disease was determined on the basis of the Hoehn and Yahr's scale.

Table 2 – Demographic data and clinical features of the patients with vascular PD (VPD) studied.

PD patient	Age (years)	Sex	Years since diagnosis	Most affected upper limb	UPDRS (upper limb)	UPSIT score	MMSE score	Clinical signs						
								T	R	B	A	P	O	F
1	66	F	3	L	4.4	35	30	–	–	–	–	–	–	–
2	68	F	3	L	3.3	37	30	–	–	–	–	–	–	–
3	68	M	2	L	6.2	32	29	L	–	–	–	–	–	–
4	69	F	4	L	4.8	34	30	R	–	+	–	–	–	–
5	66	M	4	R	5	36	30	L	+	+	+	–	–	–
6	70	F	3	R	8	36	29	L	–	+	–	–	–	–
7	72	F	2	L	3	35	28	R	+	+	–	–	–	–
8	68	F	2	L	6	31	30	–	–	+	–	–	–	–
9	69	M	3	L	4	37	30	–	–	L	–	–	–	–
10	71	M	2	L	8	35	30	–	–	+	+	–	–	–
11	67	M	2	L	10	34	29	R	–	+	+	–	–	–
12	69	F	1	L	3	33	29	–	–	+	–	–	–	–

Patient	Onset	Clinical features	MRI	Vascular risk factors	L-dopa response
1	Insidious	Hemiparkinsonism following stroke, bradykinesia	DWML, PWML	Hypertension	Not tried
2	Insidious	Asymmetric parkinsonism with tremor, bradykinesia	DWML, PWML	Hypertension	Good
3	Acute	Hemiparkinsonism following stroke, bradykinesia	Bilateral GP lesion	Hypertension, diabetes	Not tried
4	Acute	Asymmetric parkinsonism with tremor, bradykinesia	Bilateral GP lesion	Hypertension, stroke	Not tried
5	Acute	Shuffling gate, bradykinesia	Lesion contralateral LN	Stroke	Not tried
6	Acute	Hemiparkinsonism following stroke, bradykinesia	Bilateral GP lesion	Hypertension, stroke	Poor
7	Insidious	Hemiparkinsonism following stroke, bradykinesia	DWML, PWML	Family history of stroke	Good
8	Acute	Hemiparkinsonism following stroke, bradykinesia	Lesion contralateral LN	Hypertension	Not tried
9	Insidious	Shuffling gate, asymmetrical parkinsonism with rest tremor, bradykinesia	DWML, PWML	Hypertension	Good
10	Acute	Hemiparkinsonism following stroke, bradykinesia	Lesion contralateral GP	Stroke	Not tried
11	Insidious	Lower body parkinsonism, bradykinesia	DWML, PWML	Family history of stroke	Good
12	Acute	Hemiparkinsonism following stroke, bradykinesia	Lesion contralateral GP	Stroke	Not tried

Conventions as for Table 1.
Note. DWML, deep subcortical white matter (bilaterally); GP, globus pallidus; LN, lentiform nucleus; PWML, periventricular white matter lesions (bilaterally).

describes the odor. The maximum score, corresponding to normosmia, is 40. According to the literature, normal values decrease with age and are lower in men (Doty et al., 1984). All the participants showed right-handed dominance (Edinburgh Inventory; Oldfield, 1971). The experimental sessions were individual and lasted an hour. Approved by the ethics committee of the University of Padova (Protocol number 42), this study was carried out in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all of the participants.

2.2. *Stimuli and apparatus*

The visual stimuli (i.e., targets) consisted of four plastic objects grouped on the basis of their natural sizes: large (apple, orange) and small (almond, strawberry). Imitation rather than real fruit was used in order to maintain consistent visual features and sizes throughout the experimentation period. Odors evoking strawberries, almonds, oranges, and apples were obtained by mixing 6000 μl of propylene glycol and 180 μl (3%), 60 μl (1%), 420 μl (7%), and 45 μl (.75%) of the specific compound, respectively. A custom-built, computer-controlled olfactometer (Department of Experimental Psychology, University of Oxford) was used to deliver the odor stimulus or odorless air. Each odor generator consisted of a glass boat containing one of the four odor stimuli. A fifth glass boat containing propylene glycol was used to deliver odorless air. Passed over the odor solutions and propylene glycol at a flow rate of 8 l/min, the air mixture was delivered to a face mask attached to Teflon tubing (Fig. 1). Data from a pilot

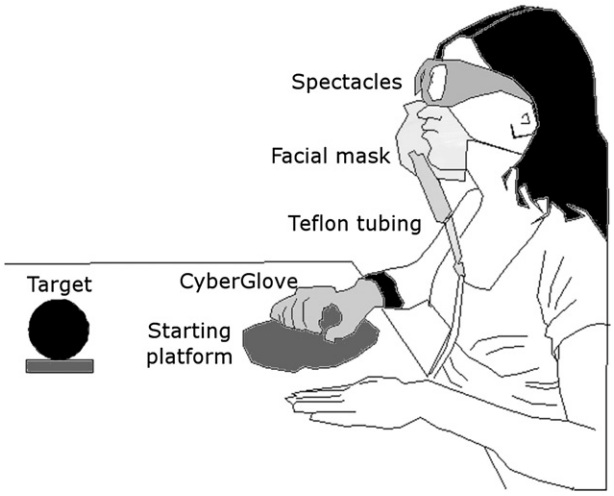

Fig. 1 – Graphical representation of the experimental set-up. Legends indicate the relevant details.

study showed that the objects associated with the considered odor stimuli were all correctly identified by those individuals who were not anosmic. For the IPD patients the percentage of correct association between odor and visual target was around chance level (52%). Further, the odor stimuli associated to the targets were judged on a 10-cm visual analogous scale ranging from not-perceivable/intense/familiar-at-all to extremely-perceivable/intense/familiar. The odor stimuli were judged as equally perceivable (almond: 8.87; strawberry: 9.01, apple: 8.94; orange: 9.03), equally intense (almond: 5.89; strawberry: 5.89, apple: 6.40; orange: 6.44), and equally familiar (almond: 7.54; strawberry: 7.70, apple: 6.98; orange: 7.33) by all normosmic participants. No significant differences were found across controls and VPD groups ($p_s > .05$). On average, IPD patients judged the odors as equally perceivable (almond: 1.76; strawberry: 2.03, apple: 1.85; orange: 1.94), equally intense (almond: 1.56; strawberry: 1.82, apple: 1.53; orange: 1.67), and equally familiar (almond: 6.89; strawberry: 6.97, apple: 7.04; orange: 7.12), but their ratings were significantly lower than those expressed by normosmic controls and VPD participants ($p_s < .05$). At the beginning of the session each individual was asked to place his/her right hand on a starting platform within which a pressure sensitive switch was embedded (i.e., starting switch). The platform was designed with slight convexities dictating a natural flexed posture of the fingers (Fig. 1). The target object was placed on a second pressure sensitive switch (i.e., the ending switch) embedded within the working surface (Fig. 1). To control vision, the participants were asked to wear spectacles fitted with liquid crystal lenses (Translucent Technologies Inc., Toronto, Ontario, Canada) which changed from opaque to transparent (Fig. 1). Participants were told that pressing the starting switch, which would determine visual availability of the target (i.e., opening of the spectacles), should correspond to the onset of the reaching movement toward the target. Movement amplitude was measured at the time the ending switch was released as the object was being grasped. Movement time was calculated as the interval between the times that the starting and ending switches were pressed.

2.3. Recording techniques

Hand kinematics was measured by a flex sensor glove (CyberGlove, Virtual Technologies, Palo Alto, CA, USA) worn on the participant's right hand (Fig. 1). The sensors' linearity was .62% of maximum nonlinearity over the full range of hand motion. The sensors' resolution was .5° remaining constant over the entire range of joint motion. The output of the transducers was sampled at 12-msec intervals.

2.4. Procedures

At the beginning of the session the participant was positioned with his/her elbow and wrist resting on a flat surface, the forearm horizontal, the arm was oriented in a natural para-sagittal plane passing through the shoulder, and the right hand was placed in a pronated position with the palm toward the working surface on the starting switch. The target was aligned with the participant's body midline, located 33 cm from the hand starting position to the left of the participant's right shoulder (Fig. 1). The sequence of events for each trial was the following: (1) once correctly positioned, the participant's vision was occluded while the target was being placed on the working surface; (2) an auditory signal was sounded (850 msec duration, 65 dB sound pressure, 800 Hz frequency) indicating that the odor was about to be released. This signal also served as a prompt for participants to breath in; (3) after 3 sec a similar signal was sounded to indicate the odor had been released; (4) 500 msec later the signal was sounded again; (5) participants were instructed to reach toward, to grasp, and to lift the target when they heard the third tone. Sufficient time interval (10 sec) was scheduled between trials to permit the odor to dissipate (Hummel et al., 1996). This sequence of events was adopted because findings in the literature have indicated that the effects of olfactory stimuli on reach-to-grasp kinematics are maximized when the olfactory stimuli/cues are presented slightly before the object is visually grasped (Tubaldi et al., 2008a). The participants were instructed to reach for the object at a natural speed and not to grasp it by the stem. An experimenter visually monitored all of the trials to ensure that participants complied with instructions. The experimenter noted that the participants naturally grasped the small objects between the thumb and the index, at times also with the help of the middle fingers, while the large objects were grasped using the thumb and the rest of the fingers. The task was performed under six experimental conditions: (1) congruent-large (LL) condition: an odor associated with a large size object was presented before a reach-to-grasp movement toward a large target was initiated; (2) congruent-small (SS) condition: an odor associated with a small size object was presented before a reach-to-grasp movement toward a small target was initiated; (3) incongruent small (SL) condition: an odor associated with a small size object was presented before a reach-to-grasp movement toward a large target was initiated; (4) incongruent large (LS) condition: an odor associated with a large size object was presented before a reach-to-grasp movement toward a small target was initiated; (5) no odor-large (NoL) condition: odorless air was released before a reach-to-grasp movement toward a large target was initiated; (6) no odor-small (NoS) condition: odorless air was

released before a reach-to-grasp movement toward a small target was initiated.

Odor-target combinations for each experimental condition are outlined in Fig. 2. Each participant took part in a total of 48 trials (eight for each experimental condition) which were presented in randomized order.

2.5. Dependent measures

In accordance with previous reports assessing the effects of olfactory stimuli on movement performance (Castiello et al., 2006; Tubaldi et al., 2008a, 2008b), the dependent variables specifically relevant to test our hypothesis were movement time and maximum grip amplitude. These variables were considered particularly appropriate to test our hypotheses because PD patients typically show slowness of movement (bradykinesia) and hand opening alterations (hypometria) when asked to perform reach-to-grasp movements (Rand and Stelmach, 2005) while other aspects of kinematic parameterization appear to be largely unaltered with respect to neurologically healthy participants (e.g., Castiello et al., 1993; Tresilian et al., 1997).

2.6. Data analysis

For each dependent measure, a mixed analysis of variance (ANOVA) with 'group' (IPD, VPD, controls) as between-subject factor as well as 'olfactory condition' (congruent, incongruent, control) and 'target size' (large, small) as within-subject factors was performed. The main assumptions behind this statistical model (i.e., normality and sphericity) were checked before running the ANOVA. The Kolmogorov–Smirnov test showed that the normality assumption was satisfied (α-level: $p < .05$). The Mauchly test showed that the sphericity assumption was not violated. Results from the ANOVA performed on the slope absolute values were assessed through post hoc comparisons using t-tests. The Bonferroni correction was applied when requested (α-level: $p < .05$). Preliminary analyses were performed to assess possible gender differences in selective odor identification between VPD and control participants. No significant effect was detected with reference to gender ($p > .05$). Because on the basis of previous literature (e.g., Castiello et al., 2006), we expected odor 'size' to be the main determinant as to influence the considered dependent variables, we wanted to exclude the presence of a possible 'semantic' effect. Thus, we compared the obtained values in terms of size congruent (e.g., orange–apple) and semantic congruent (e.g., orange–orange) pairs. This was done for both the small and the large targets. No significant differences were detected ($p_s > .05$). Therefore the data were collapsed across gender and semantic/size congruency.

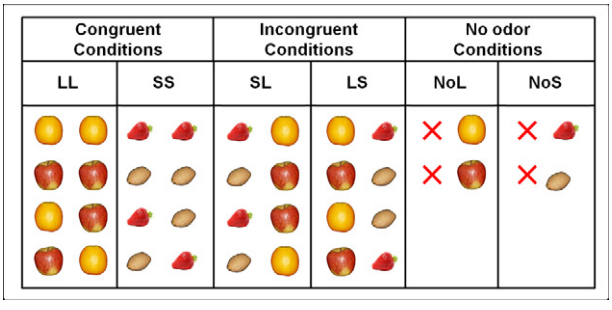

Fig. 2 – From left to right, columns report the congruent, incongruent and no odor experimental conditions resulting from the combination of olfactory (first drawing of each couple within a column) and visual (second drawing of each couple within a column) stimulations. LL: congruent-large condition; congruent-large: congruent-small condition; SL: incongruent large condition; LS: incongruent small condition; NoL: no odor-large condition; NoS: no odor-small condition.

3. Results

3.1. Movement time

The main effect of group was significant [$F(2,22) = 171.20$, $p < .0001$, $\eta_p^2 = .94$]. Post hoc comparisons revealed that movement times were longer for both the IPD and the VPD than for the controls ($p_s < .0001$; 1598, 1587 and 896 msec, respectively). The movement times of the IPD and the VPD were not significantly different ($p > .05$; Fig. 3). As indicated by the main effect of target size [$F(1,11) = 847.14$, $p < .0001$, $\eta_p^2 = .99$], movement times were shorter for the larger than for the smaller targets (1329 *vs* 1392 msec). The main effect of olfactory condition was also significant [$F(2,22) = 203.68$, $p < .0001$, $\eta_p^2 = .95$]. Movement times for the congruent condition were significantly shorter than for the no odor and the incongruent conditions ($p_s < .0001$; 1288, 1354 and 1439 msec, respectively). A significant difference was also found in movement times when the no odor and the incongruent conditions were compared ($p < .0001$). These results indicate that PD patients are slower than controls and that congruent odors evoke shorter movement times, while incongruent odors determine longer ones. The no odor condition was associated with intermediate values. The similarity of the revealed effects across the three groups is highlighted in Fig. 3. The two-way interaction 'group by condition' was significant [$F(4,44) = 14.32$, $p < .0001$, $\eta_p^2 = .57$]. Post hoc contrasts revealed that for all conditions movement time was significantly slower for both the PD groups (IPD and VPD) than for the control group. The two-way interactions 'group by dimension' [$F(2,22) = 2.037$, $p > .05$, $\eta_p^2 = .16$], and 'condition by dimension' [$F(2,22) = 28.389$, $p > .05$, $\eta_p^2 = .01$] were not significant. Similarly, the three-way 'interaction group by olfactory condition by target size' did not reach the significance level [$F(4,44) = 100.40$, $p > .05$, $\eta_p^2 = .03$].

3.2. Maximum grip amplitude

The main effect of group was significant [$F(2,22) = 44.73$, $p < .0001$, $\eta_p^2 = .80$] as both the IPD and the VPD patients showed smaller grip amplitudes with respect to the controls ($p < .0001$; 81, 80 and 90 mm, respectively). The maximum grip amplitude did not differ in the IPD and VPD patients ($p > .05$). The main effect of target size was also significant [$F(2,22) = 1299.03$, $p < .0001$, $\eta_p^2 = .99$]. The maximum grip

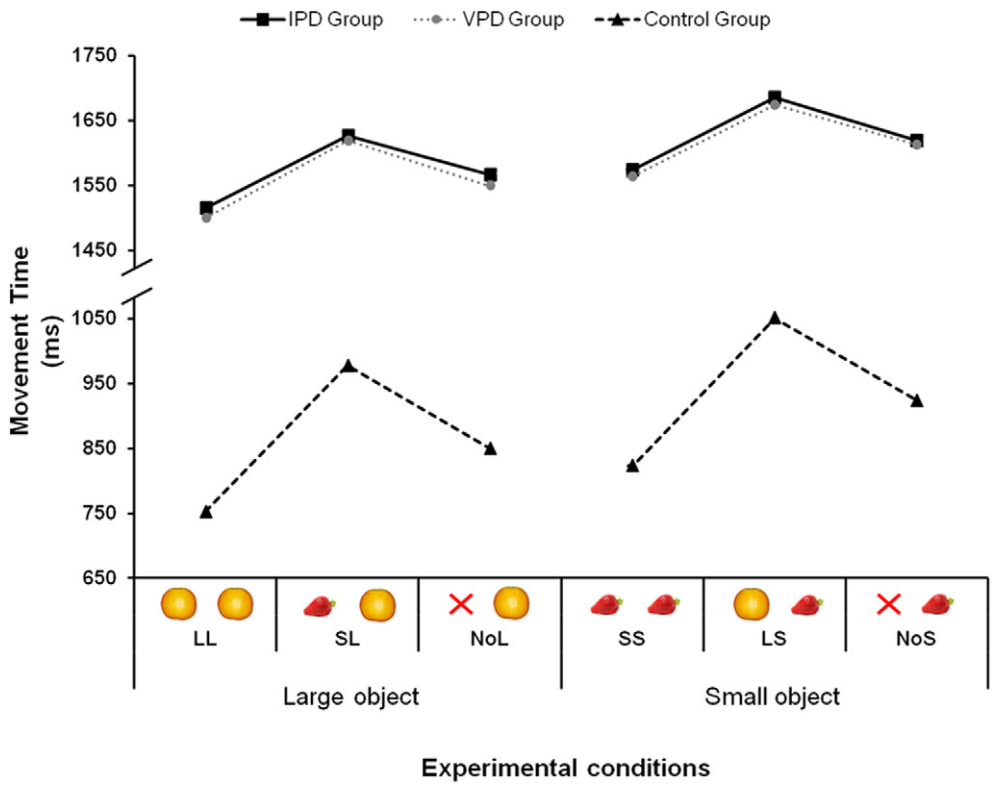

Fig. 3 – Lines represent the duration of the reach-to-grasp movement expressed in msec for the IPD (black solid line), VPD (gray dotted line) and healthy participants (black dashed line) for the six experimental conditions tested (from left to right: congruent, incongruent, no odor condition for the large and for the small targets, respectively).

amplitude was wider for the larger than for the smaller targets (92 *vs* 75 mm). Analysis of the main effect of olfactory condition [$F(2,22) = 43.29$, $p < .0001$, $\eta_p^2 = .80$] indicated that the maximum grip amplitude was smaller for the no odor than for the incongruent and congruent conditions ($p_s < .0001$; 82, 84 and 85 mm, respectively). The two-way interactions 'group by condition' [$F(4,44) = 38.99$, $p < .0001$, $\eta_p^2 = .78$], 'group by dimension' [$F(2,22) = 77.195$, $p < .0001$, $\eta_p^2 = .88$], and 'condition by dimension' [$F(2,22) = 647.54$, $p < .0001$, $\eta_p^2 = .98$] were significant. The three-way interaction 'group by olfactory condition by target size' was also significant [$F(4,44) = 24.16$, $p < .0001$, $\eta_p^2 = .69$]. In the following sections we shall consider only the highest order interaction (Maxwell and Delaney, 2003).

3.2.1. *Large targets*

Post hoc comparisons indicate that in both PD groups the maximum grip amplitude was greater for the congruent than for the no odor condition ($p < .0001$; Fig. 4). For incongruent conditions in which a 'small' odor was released before a large target was presented, the maximum grip amplitude was smaller in the PD patients compared to that for the no odor and congruent conditions ($p < .0001$; Fig. 4). There were no significant differences across the congruent and the no odor conditions ($p > .05$; Fig. 4), but the maximum grip amplitude was smaller for the incongruent than for the no odor and congruent conditions ($p < .0001$; Fig. 4).

3.2.2. *Small targets*

Post hoc comparisons indicate that in both PD groups the maximum grip amplitude was greater for the congruent than for the no odor condition ($p < .0001$; see Fig. 4). For the incongruent condition in which a 'large' odor was delivered before a small target was presented, the maximum grip amplitude in the PD patients was wider than it was for the no odor and congruent conditions ($p < .0001$; Fig. 4). There were no significant differences across the congruent and the no odor conditions in the controls ($p > .05$; Fig. 4), but the maximum grip amplitude was wider for the incongruent than for the no odor and the congruent conditions ($p < .0001$; Fig. 4).

4. Discussion

The aim of this study was to assess implicit olfactory processing in IPD patients. The results indicate that although these patients generally have severe forms of olfactory loss, they do continue to process olfactory stimuli implicitly. Just as neurologically healthy and VPD groups, IPD patients were found to be facilitated in their actions when they were exposed to an odor evoking an object that was similar in size with respect to a target. Olfactory priming, in fact, seemed to determine an improvement in bradykinesia of hand transport movement and hypometria of the grip amplitude in these

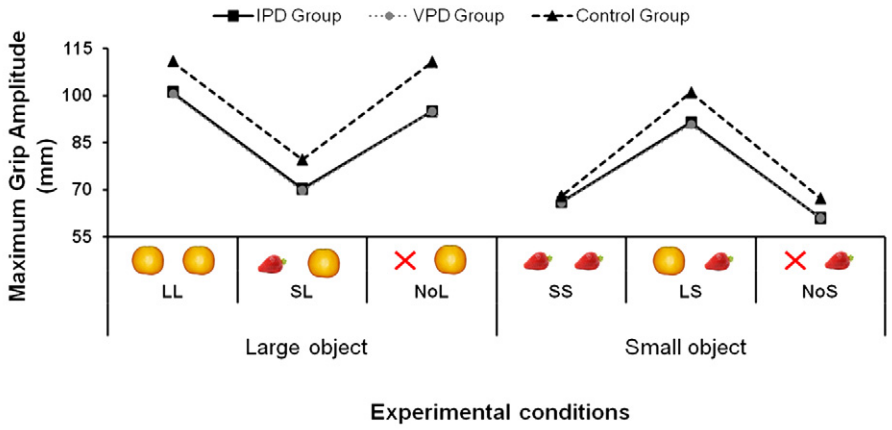

Fig. 4 – Lines represent the maximum grip amplitude expressed in mm for the IPD (black solid line), VPD (gray dotted line) and healthy participants (black dashed line) for the six experimental conditions tested (from left to right: congruent, incongruent, no odor condition for the large and for the small targets, respectively).

patients. If, instead, the odor evoked a different sized object with respect to the visual target there were interference effects in the movement pattern in the IPD patients just as in the other two groups studied.

4.1. *The effect of object size on movement kinematics*

The results concerning the conditions in which presentation of visual targets was not preceded by olfactory information also provide insight about some aspects of olfactory processing. In order to ascertain the effects of size olfactory information on movement kinematics it is necessary to demonstrate that the size of the visual target affects movement timing and grip amplitude. And, in fact, significantly different kinematic patterns were found for the two target sizes in all the groups studied. The movement time was longer and the maximum grip amplitude was reduced for smaller with respect to larger targets in both groups of PD patients (e.g., Castiello et al., 1993; Tresilian et al., 1997) as well as in the neurologically healthy participants (Jeannerod, 1984; Gentilucci et al., 1991; Jakobson and Goodale, 1992). With specific reference to the PD group, previous evidence demonstrating that their reach-to-grasp movements were slower (e.g., Castiello et al., 1993; Tresilian et al., 1997) and their maximum grip amplitude smaller (Rand and Stelmach, 2005) with respect to control participants was confirmed.

4.2. *Implicit processing of olfactory stimuli*

The results outlined here indicate that reach-to-grasp movement planning was carried out on the basis of olfactory information in all three groups studied (e.g., Castiello et al., 2006; Tubaldi et al., 2008a, 2008b). In those cases in which the size of the visual target and that of the object elicited by the olfactory stimulus did not match, the motor plan elicited by odor did not appear to be totally superseded by that later elicited by the visual target. In other words, some aspects of the motor plan implicitly elicited by an incongruent olfactory stimulus persist in the prehensile movement made to grasp the visual target. It is important to remember that in these situations the movement elicited by the olfactory stimuli is different from the one visually needed. Parallel preparations appear to be made for both types of movements: one for the visual target and one for the olfactory stimulus, and this might explain the differences found in action kinematics. Conversely, when an odor elicits a motor plan which is congruent with the plan made subsequently for the visual target, facilitation effects were noted. The hand movement plan triggered by the olfactory stimulus seems to pave the way for the plan made for the visual target. Taken together, these results are particularly important with regard to the IPD group as they demonstrate that although these patients are unable to explicitly process olfactory information, some sort of implicit olfactory processing does take place. Not only, when primed by a congruent olfactory stimulus, IPD patients are faster and better able to increase hand amplitude thus diminishing the tendency to produce movements that are slower (bradykinesia) and smaller (hypometria).

These results clearly confirm that there is some kind of olfactomotor activity in PD patients despite the fact that the hypothesis that their olfactory impairment depends at least in part on less vigorous sniffing (Sobel et al., 2000) as well as reduced responses to passive olfactory stimulation (Hawkes et al., 1999). The results presented here suggest that even though motor problems can reduce olfactomotor activity, they do not preclude odor elaboration and an appropriate behavioral reaction to olfactory cues from the external world. In this respect, it is worth noting that all the IPD participants included in the present experimental sample were functionally anosmic, which means that some sort of residual (implicit) olfactory abilities might be present.

4.3. *The dissociation of explicit and implicit olfactory processing in IPD*

These findings also evince a dissociation between explicit and implicit olfactory processing in these patients. Olfactory

deficits in PD have been described as far as odor identification, odor discrimination, odor threshold detection, and odor recognition memory are concerned (Mesholam et al., 1998; Haehner et al., 2009), even though there is considerable inconsistency in the reliability of olfactory testing (Doty et al., 1994). It is possible that some tests assessing olfactory function are unable to provide reliable results because the operational processes involved depend in part on the integrity of brain structures involved in cognition or memory, such as the hippocampus (Larsson et al., 2004; Wang et al., 2005). Odor impairment in early stages of PD has been found to correlate with hippocampal dopaminergic denervation (Bohnen et al., 2008a, 2008b). It is possible then that the implicit olfactory processing observed in IPD patients may not require conscious recollection of olfactory stimuli or the integrity of structures involved in memory functions, but on the amygdala, an area which is physically closer to the olfactory sensory modality and may not be compromised during early stages of the disease (Braak et al., 2003, 2004; Bohnen et al., 2008a, 2008b). Other possible candidate areas might be the piriform or the entorhinal cortex, which have been previously shown to be activated during the passive presentation of olfactory stimuli (Savic et al., 2000). Support to this contention comes from a study carried out by Welge-Lüssen and coworkers (Welge-Lüssen et al., 2009), who showed that the brain activity in the amygdala, parahippocampal and temporal regions was preserved in hyposmic IPD patients.

Considering the multisensory nature of the motor task presented here, it is worth noting that the amygdala – responsible for the encoding of the significance of cues – has critical interconnections with the orbitofrontal cortex (OFC), which serves as a center for appraisal, guiding adaptive goal-directed behavior based on information accessed through its connections with the amygdala as well as with other structures (Schoenbaum et al., 1998). It is possible that the effects found in the present study are mediated by an implicit olfactory encoding occurring at the level of the amygdala which is conveyed to the OFC where visual–olfactory representations are formed. This hypothesis seems to be supported by the facilitation effects found in the IPD patients when the visual and the olfactory stimuli were congruent. Neuroimaging findings (Gottfried and Dolan, 2003; Österbauer et al., 2005) and neurophysiological studies (Stein and Meredith, 1990; Rolls and Baylis, 1994; Grigor, 1995; Grigor et al., 1999; Sarfarazi et al., 1999) indicate that facilitation effects, associated with enhanced neural activity within the OFC, are obtained by manipulating the degree of correspondence between olfactory and visual stimuli.

Confirmation of a direct connection between OFC and motor areas involved in arm-hand movement control (Morecraft and Van Hoesen, 1993; Cavada et al., 2000) is of particular importance for our study in view of the well-known homology between cerebral regions underlying reach-to-grasp movements in monkeys and humans (for review see Castiello, 2005). It can be hypothesized that the corticocortical connections between OFC and motor areas affecting motor output (e.g., Bates and Goldman-Rakic, 1993) can account for the influence multisensory integration of olfactory–visual information has on motor behavior and more specifically on prehensile actions (Rossi et al., 2010). In this perspective, IPD patients' prehensile movements may be affected by the chain of neural events beginning with implicit odorant encoding occurring at the amygdala level.

Before any firm conclusion can be drawn two possible limitations of the present study should be outlined. First, the inclusion of a control group of patients with hyposmia due to an infection would have allowed to shed further light on the distinction between pure olfactory and olfactomotor effects. Second, the recording of olfactory event-related potentials (e.g., Hummel and Welge-Lüssen, 2006) might have helped in quantifying the precise extent of olfactory loss which might clarify the very nature of the explicit/implicit dichotomy in olfactory processing.

4.4. *Clinical implications*

The results presented here may have some clinical implications as to improving upper limb motor control. The residual ability to perceive olfactory stimuli and to respond subconsciously to them could hypothetically be utilized to design olfactory-based rehabilitation strategies (e.g., Kawai and Noro, 1996; Bordnick et al., 2008; Gerardi et al., 2008; Ryan et al., 2010). In particular, the present findings imply that olfaction could serve as a conditioned stimulus for some voluntary, goal-directed actions. Patients can hypothetically be conditioned, following congruent olfactory stimulation, to speed up reaching movements and to shorten or lengthen their grip amplitude. Continuous, constant practice might help make the movement automatic and facilitate the patient's performance in an ecological environment even in the absence of olfactory prompts. Future studies would seem warranted in view of this prospect.

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