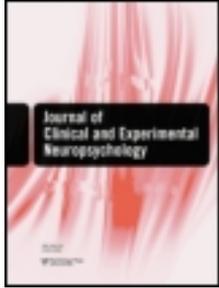


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Valentina Parma^a, Elisa Straulino^a, Debora Zanatto^a, Anna Cantagallo^b,
Roberto Tirindelli^c & Umberto Castiello^a

^a Department of General Psychology, University of Padova, Padova, Italy

^b BrainCare, Padova, Italy

^c Department of Neuroscience, University of Parma, Parma, Italy

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Implicit olfactory abilities in traumatic brain injured patients

Valentina Parma¹, Elisa Straulino¹, Debora Zanatto¹, Anna Cantagallo², Roberto Tirindelli³, and Umberto Castiello¹

¹Department of General Psychology, University of Padova, Padova, Italy

²BrainCare, Padova, Italy

³Department of Neuroscience, University of Parma, Parma, Italy

To investigate implicit olfactory abilities in a group of anosmic traumatic brain injured (TBI) patients, an olfacto-motor priming paradigm was administered. A group of matched normosmic/mildly microsmic TBI patients and a group of neurologically healthy participants served as controls. For all the groups, an interference effect was evident on the peak velocity of grip aperture when participants grasped a large target preceded by a “small” odor. The present results suggest that some form of implicit olfactory processing is preserved in TBI patients even when diagnosed as anosmic on the basis of explicit olfactory testing.

Keywords: Head trauma; Olfaction; Implicit processing; Reach to grasp; Kinematics.

INTRODUCTION

Head trauma (or traumatic brain injury, TBI) is a diffuse cause of disability (and death) in the adult population (Bruns & Hauser, 2003; Costanzo & Zasler, 1991). TBI is a multifaceted pathological phenomenon. From a physical perspective, it results from the effect of mechanical forces occurring at the moment of trauma—such as laceration of brain tissue, diffuse white matter damage, intracerebral hemorrhage, or hematoma (primary mechanisms; Adams et al., 1989)—or in a second moment as consequences of primary mechanisms—as in the case of hypoxia, intracranial hypertension, or cerebral edema (secondary mechanisms; Pitts & McIntosh, 1990). From a clinical perspective, TBI patients incur deficits in cognitive (memory, attention, language, executive functions; National Institutes of Health, 1999), psychosocial (emotion regulation; Cunningham et al., 1999), and sensorimotor domains (visual, auditory, proprioceptive, olfactory, and gustatory; Lynch, 1986). Of relevance, the investigation of sensory impairment following head trauma has not been confined

to the most studied sensory modalities (e.g., vision, audition, and touch), but it has also been extended to the chemical senses. As a result, head trauma is now paradigmatically remembered as an example of pathology presenting moderate or severe olfactory disturbance.

Posttraumatic olfactory loss (PTOL) is the third most common etiology for olfactory disorders (Collet, Grulois, Bertrand, & Rombaux, 2009), and it accounts for 4–15% of the chemosensory disturbance in the general population (Doty et al., 1997). PTOL has usually been reported following frontal basal injuries as well as occipital blows (Doty et al., 1997; Fujii, Fukazawa, Takayasu, & Sakagami, 2002; Sumner, 1964). Differently from other pathologies, such as multiple sclerosis and Parkinson's disease (Meshulam, Moberg, Mahr, & Doty, 1998), the likelihood of completely losing the ability to smell is directly correlated to the severity of the trauma and to the mechanical characteristics of the impact (e.g., strong acceleration/deceleration of the head). The most extreme forms of PTOL are presumably due to a coup–countercoup mechanism responsible for the shearing of olfactory nerves

Address correspondence to Valentina Parma, Dipartimento di Psicologia Generale, Università di Padova, via Venezia 8, 35131 Padova, Italy (E-mail: valentina.parma@unipd.it).

penetrating the cribriform plate (Zusho, 1982) or to contusions or secondary hemorrhages within the central olfactory areas (Reden et al., 2006).

The number of patients complaining of olfactory loss is higher in those presenting frontal and occipital lobe insults than in patients presenting traumatic lesions outside these areas (Doty et al., 1997). However, as a general rule, patients have poor awareness of their olfactory dysfunctions, especially when they are associated with other neurological deficits (Callahan & Hinkebein, 2002).

PTOL prognosis may vary widely. Overall, it results in a distorted perception of flavors, and its iatrogenic effect has been documented in terms of decreased quality of life, safety, social relationships, and dietary intake (Corydon Hammond, 2007). When possible, recovery occurs, on average, within the first year from the injury even though recent research suggests that delayed improvement of olfactory function might occur (London et al., 2008). Nevertheless, the likelihood of recovery to functional smell abilities hinges upon the integrity of the brain regions involved in olfactory processing.

At a neural level, head trauma presents multiple and various landscapes, which cannot be traced back to regular patterns, as evident for other pathologies (e.g., Braak et al., 2003). Nevertheless, the dispersed nature of the olfactory system within cortical and subcortical regions facilitates the fact that traumatic lesions involve, at least in part, the areas concerned with olfactory processing. Evidence from neuroimaging studies indicate that a damage at the level of eminent olfactory regions, such as entorhinal cortex or orbitofrontal cortex, is associated with poor performances at olfactory behavioral tasks (Atighechi, Salari, Baradarantar, Jafari, Karimi, & Mirjali, 2009; Bonanni et al., 2006; Fujiwara, Schwartz, Gao, Black, & Levine, 2008; Geisler, Schlotfeldt, Middleton, Dulay, & Murphy, 1999; Haxel, Grant, & Mackay-Sim, 2008; Mann & Vento, 2006; Roberts, Sheehan, Thurber, & Roberts, 2010; Sandford et al., 2006; Yousem, Geckle, Bilker, McKeown, & Doty, 1996). It must be said, however, that the present bulk of studies, as well as those only considering patients' performance at olfactory psychophysical tests (Callahan & Hinkebein, 1999, 2002; De Kruijck et al., 2003; Fortin, Lefebvre, & Ptito, 2010; Green & Iverson, 2001; Green, Rohling, Iverson, & Gervais, 2003; Landis et al., 2010; Sigurdardottir, Jerstad, Andelic, Roe, & Schanke, 2010; Swann, Bauza-Rodriguez, Currans, Riley, & Shukla, 2006), applied testing methods that require some specific cognitive functions to be intact. To date, to succeed in the completion of tests such as the University of Pennsylvania

Smell Identification Test (UPSIT, Doty, Shaman, & Dann, 1984) and the Sniffin' Sticks Extended Test (Kobal et al., 1996), unharmed verbal and memory skills are needed (Olsson, Jonsson, & Faxbrink, 2002). But TBI patients are frequently diagnosed with language and memory disturbance (Jenett & Teasdale, 1981; Teasdale & Mendelow, 1984), indicating that the conclusions stemming from the abovementioned studies should be taken into account with a certain degree of caution.

A point worth noting is that, still in everyday life, it is hard to correctly label the name of an odor (de Wijk & Cain, 1994; Engen, 1987). Our daily experience suggests that odors are mingled within each other, making it difficult even to discriminate—without naming them—the odors we simultaneously encounter. These are examples of the fact that the learning experience of dealing with odors primarily occurs unintentionally and subliminally (Issanchou, Valentin, Sulmont, Degel, & Koster, 2002; Wilson & Stevenson, 2006). Together with the scattered nature of olfactory circuits, this might indicate that different, and partially independent, mechanisms of odor processing might exist. Then, it is reasonable to think that explicit (language-mediated) and implicit (nonlinguistic) forms of olfactory processing coexist in order to cover all the aspects of the multifaceted world of odors.

To the best of our knowledge, no studies have yet investigated whether (and, possibly, how) implicit forms of olfactory processing take place in TBI patients. Recent research concerning the role of olfaction in sensorimotor control might help this endeavor (Castiello, Zucco, Parma, Ansuini, & Tirindelli, 2006; Tubaldi, Ansuini, Demattè, Tirindelli, & Castiello, 2008; Tubaldi, Ansuini, Tirindelli, & Castiello, 2008). In these experiments, participants were presented with an odor evoking either a small or a large object. Then, they were requested to reach and grasp either a small or a large visual target. For the “incongruent” condition, the visual target required a grip type that differed from that called by the “odor” object. As an example, a small to-be-grasped target could be a strawberry, calling for a precision grip (e.g., the opposition of the thumb and the index finger) whereas the odor anticipating movement initiation could be that of a large odor (e.g., orange) calling for a whole hand grip (e.g., the opposition of the thumb to all the other fingers). For this condition, the results indicated that kinematic parameterization for the olfactory “object” leaked in and affected how the grip for the visual object was shaped during reaching. In terms of specific kinematical variables, maximum grip aperture was larger, and peak velocity of grip aperture (i.e.,

how fast the hand opened to a maximum, unpublished data) was higher than when the small target was grasped in the absence of the “incongruent” olfactory stimulation. The opposite pattern of results occurred when the to-be-grasped target was “large” (e.g., an orange), and the odor was “small” (e.g., a strawberry). In these circumstances, maximum grip aperture was smaller, and peak grip velocity was lower than when the same target was grasped in the absence of the “incongruent” olfactory stimulation. For the “congruent” condition, instead, the visual and the olfactory objects were of a similar size. In these circumstances, maximum grip aperture for the visual target was more tuned to the size of the object, and peak velocity of grip aperture was faster than when the same target was grasped in the absence of any olfactory stimulation. This effect was interpreted in terms of a cross-modal optimization/facilitation effect.

The aforementioned interference and facilitation effects were partly explained in terms of action-based attentional mechanisms that may serve to select the target from competing distractors (Castiello, 1999; Tipper, Howard, & Houghton, 1998). In these terms, the visual target and the olfactory distractor both evoke grasping representations that can interact in either a mutually suppressive/competitive or facilitating fashion in whatever modality they are presented. Interference is thus the result of the competition between the visual target and the potential distractors’ action representation. Accordingly, facilitation is the result of a “size” congruency between the visual target and the potential distractors’ action representation.

Altogether, such evidence indicates that, although the olfactory stimulus was irrelevant for fulfilling the task, it was nevertheless implicitly elaborated in motor terms such as to interfere with, or facilitate, the motor plan established for the to-be-grasped target.

In this connection, we hypothesized that, if some sort of implicit processing of olfactory stimuli is preserved in TBI patients, then this might be reflected in terms of either motor behavior interference or facilitation. Thus, we asked a group of anosmic TBI (aTBI) patients to execute reach-to-grasp movements towards visual targets following the presentation of olfactory cues, which could be size congruent, incongruent, or nonexistent. For comparison purposes, the performance of this group was matched with the performance of two control groups: a group of TBI patients showing similar cognitive and psychosocial abilities to those of the aTBI patients, but without severe olfactory deficits, and a group of neurologically healthy participants.

If implicit olfactory processing is preserved in aTBI patients, we expect that this group would be affected by task-irrelevant odors as well as normosmic/mildly microsmic TBI (nTBI) patients and healthy control groups. On the basis of previous literature (e.g., Tubaldi, Ansuini, Tirindelli et al., 2008), we expect these effects to be evident on key kinematic variables concerned with the grip phase (i.e., maximum grip aperture and peak grip aperture velocity).

METHOD

Participants

The study included 12 patients diagnosed with severe head trauma on the basis of the Glasgow Coma Scale (GCS = 3 to 8; Teasdale & Jennett, 1974). Inclusion criteria were: Level of Cognitive Functioning (LCF) Scale score > 5 (Gouvier, Blanton, LaPorte, & Nepomuceno, 1987); normal vision or corrected to normal vision; right-handed. Exclusion criteria were: participants presenting aphasia, apraxia, ataxia, drugs abuse, and previous neurological disease. Twelve age- and gender-matched controls were recruited for comparison purposes. The sample was composed of 83% males. Participants were divided into three groups (Table 1) considering their olfactory abilities as determined by the scores obtained at the UPSIT (Doty et al., 1984; Appendix C). The aTBI group included 6 participants (mean age = 38.68 years, $SD = 9.12$ years); 6 patients formed the nTBI group (mean age = 39.46 years, $SD = 8.38$ years). Both patients and controls were tested with the (a) Beck Depression Inventory–II (BDI–II; Beck, Steer, & Brown, 1996); (b) Beck Anxiety Inventory (BAI; Beck & Steer, 1990); (c) Raven’s Progressive Matrices (PM; Raven, 1938/2003); (d) Trail Making Test (TMT; Reitan, 1955); and (e) verbal span (Spinnler & Tognoni, 1987) to check for depression, anxiety and/or cognitive impairment at the time of olfactory testing. When compared to neurologically healthy participants, aTBI patients reported significantly higher depressive symptoms (BDI–II) and poorer performance at the TMT, which gives indications on the attentional/executive abilities of participants ($p < .05$). No significant difference was found when comparing the anosmic group with the normosmic/mildly microsmic groups ($p > .05$) on the other measures administered. The Edinburgh Handedness Inventory (Oldfield, 1971; Appendix D) was used in order to determine hand preference. Finally, a questionnaire was administered to all participants to evaluate

TABLE 1
Demographic data and clinical features of the traumatic brain injured patients and the healthy participants

Group	Age (years)	Gender	Education (years)	UPSIT score (raw score)	BAI (percentile)	BDI-II (percentile)	B-A TMT (ES)	CPM Raven (ES)	Verbal span (raw score)
aTBI	46	M	10	7	<85	>99	3	2	4
	30	M	13	8	<85	<85	0	4	5
	33	M	13	13	<85	>99	1	4	4
	51	M	17	17	<85	>95	4	4	5
	30	F	18	20	85–90	<85	3	4	6
	32	M	8	20	<85	85–90	3	4	5
	29	M	13	25	85–90	<85	4	4	4
	39	M	13	25	<85	85–90	3	4	6
	38	F	18	27	<85	<85	1	4	5
	38	M	18	29	<85	<85	2	4	5
	40	M	18	28	<85	<85	1	4	5
	49	M	7	35	<85	<85	4	4	5
Control	29	M	13	26		<85	4	4	4
	34	M	18	28	<85	<85	3	4	5
	52	M	18	30	<85	<85	4	4	5
	56	M	8	30	<85	<85	4	4	6
	32	M	18	31	<85	<85	3	3	3
	51	M	8	32	<85	<85	4	4	5
	39	M	18	33	<85	<85	3	4	5
	35	F	18	34	<85	<85	3	4	5
	40	M	18	36	<85	85–90	3	4	6
	37	M	18	37	<85	<85	3	4	7
	29	F	13	38	<85	<85	3	4	6

Note. aTBI: anosmic traumatic brain injured patients; nTBI: normosmic/mildly microsmic traumatic brain injured patients; control: neurologically healthy control participants; M = males; F = females; UPSIT: University of Pennsylvania Smell Identification Test; BAI: Beck Anxiety Inventory; BDI-II = Beck Depression Inventory; ES = equivalent score; B-A TMT = Trail Making Test Version B-A; CPM = Color Progressive Matrices.

the previous history of nasal disease and smoking habits and the current subjective status of olfactory functions (adapted from Zucco, Amodio, & Gatta, 2006; Appendix A). All participants were naïve as to the purpose of the investigation and gave informed written consent to participate in the study. The experimental procedures were approved by the Institutional Review Board at the University of Padova in accordance with the Declaration of Helsinki.

Stimuli

The visual stimuli consisted of four plastic objects grouped on the basis of their natural size: large (apple, orange) and small (almond, strawberry). Plastic objects were used in order to maintain consistent visual attributes and sizes similar throughout the period of experimentation. The odor stimuli corresponded to the target stimuli described above. Odor solutions of strawberry, almond, orange, and apple were obtained mixing 6,000 μ l of propylene glycol—a substance that is not considered irritant or hazardous at the concentration used here (Occupational Safety & Health Administration, OSHA, 1998)—and 180 μ l (3%), 60 μ l (1%),

420 μ l (7%), and 45 μ l (0.75%) of the specific odorant compound, respectively. The fruit odors were rated as isointense to each other ($p < .05$)—but significantly more intense than propylene glycol ($p > .05$)—by 43 participants, who smelled the odors for 3 s and judged the perceived intensity of each stimulus on a 10-cm visual analogous scale anchored to “not intense at all” to “extremely intense” polarities. At the end of the experimental session, all the participants were asked to rate the odors 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: 8.66; strawberry: 8.92; apple: 8.74; orange: 8.81), equally intense (almond: 5.88; strawberry: 5.82; apple: 5.76; orange: 6.03), and equally familiar (almond: 7.42; strawberry: 7.74; apple: 7.39; orange: 7.81) by all normosmic participants. No significant differences were found across controls and nTBI participants ($ps > .05$). On average, aTBI patients rated the odors as equally perceivable (almond: 1.93; strawberry: 2.11; apple: 2.05; orange: 2.03), equally intense (almond: 1.99; strawberry: 1.74; apple: 1.82; orange: 1.82), and equally familiar (almond: 7.03; strawberry: 6.84;

Congruent Conditions		Incongruent Conditions		No odor Conditions	
LL	SS	SL	LS	NoL	NoS
					
					
					
					

Figure 1. 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; SS: congruent small condition; SL: incongruent large condition; LS: incongruent small condition; NoL: no odor large condition; NoS: no odor small condition.

apple: 7.13; orange: 7.05), but their judgments were significantly lower than those expressed by normosmic controls and nTBI participants ($ps < .05$). As depicted in Figure 1, the visual/olfactory stimuli combinations produced six experimental conditions: (a) congruent large (LL), in which both the odor and the visual target evoked a large object (e.g., orange–apple); (b) congruent small (SS), in which both the odor and the visual target evoked a small object (e.g., strawberry–almond); (c) incongruent large (LS), in which the odor evoked a large object but the visual target evoked a small object (e.g., orange–almond); (d) incongruent small (SL), in which the odor evoked a small object, and the visual target evoked a large object (e.g., strawberry–apple); (e) control large (NoL), in which the odor stimulus was odorless air, and the visual target evoked a large object (e.g., air–apple); and (f) control small (NoS), in which the odor stimulus was odorless air, and the visual target evoked a small object (e.g., air–almond).

Apparatus

A custom-built computer-controlled olfactometer was used to deliver the odor stimuli or odorless air. Each of the four to-be-delivered olfactory stimuli was contained in one glass boat. As to deliver odorless air, a fifth glass boat contained propylene glycol. The air entered the glass boats at a flow rate of 8 l/min, and the resulting odorous and odorless air were delivered to participants via Teflon tubing to a facial mask.

Movements were recorded by means of a three-dimensional motion analysis system (SMART-D; BTS, Garbagnate Milanese, Italy) equipped with six infrared cameras (frequency: 140 Hz) recording the position of three passive markers (diameter = 0.25 cm). Markers were fastened using double-sided tape to (a) the wrist, (b) the tip of the index finger, (c) the tip of the thumb of the participants' right hand, and (d) the plastic object. Coordinates of the markers were reconstructed with an accuracy of 0.2 mm over the field of view. The standard deviation of the reconstruction error was 0.2 mm for the vertical (Y) and horizontal (X and Z) axes. Data were reconstructed, filtered (10 Hz), and analyzed with the SMART-D analyzer software.

Vision was controlled using spectacles fitted with liquid crystal lenses that rendered the target visually accessible by changing from opaque to clear (Plato Technologies, Toronto, Canada). At the beginning of each trial, participants placed their right hand on a starting platform within which a pressure sensitive switch was embedded. Relevant kinematic parameters of the manipulation phase of the reach-to-grasp movement, such as peak velocity of grip aperture, were analyzed.

Procedure

The target was aligned with the participant's body midline and located at a 33-cm distance from the hand starting position. The right hand of each

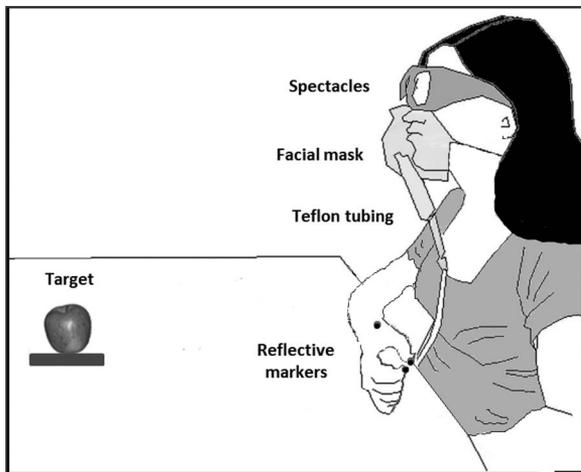


Figure 2. Graphical representation of the experimental set-up. Legends indicate the relevant details.

participant rested on a starting pad with the index finger and the thumb gently opposed (Figure 2). The sequence of events for each trial was as follows: (a) Vision was occluded before (500 ms) the target was positioned on the working surface; (b) an auditory tone indicated odor delivery; (c) after 3,000 ms, a similar tone indicated the offset of odor delivery; (d) following a 500-ms interval the tone was presented again; (e) upon hearing the tone, participants were instructed to reach towards, grasp, and lift the visual target. We instructed the participants to reach at a natural speed and not to grasp the object by the stem. The experimenter visually monitored each trial to ensure participant's compliance to these requirements. Participants naturally grasped the small visual targets between the thumb and the index (precision grip) and, occasionally, the middle finger and the large visual targets opposing the thumb with all the other fingers (whole hand grip). In order to evaluate how participants grasped the targets, a pretest session was executed. Participants performed a total of 48 trials (12 for each experimental condition), which were presented in randomized order within four blocks.

Dependent variables and data analysis

By following a hypothesis-driven approach, kinematic analysis was confined to the parameters characterizing the grip phase of the action. These variables were those that have been most effective in revealing the effects of task-irrelevant information upon the unfolding of grasping movements (Castiello, 1999; Castiello et al., 2006). Maximum grip aperture was studied by analyzing the maximum distance in millimeters between the markers located on the tip of the thumb and the index finger. The time of maximum grip aperture was the point

in time at which the thumb–index finger opening was the largest. The peak velocity of grip aperture was calculated as the maximum velocity of the thumb–index opening during the grasping time. The time of peak velocity of grip aperture corresponded to the point in time at which the velocity of distancing the thumb and the index finger reached its maximum value. Grasping time was calculated as the time from the initiation of fingers opening and the “stable” closure of the fingers around the object. The frame corresponding to the beginning of the movement was selected after verifying that the marker displacement increased in each of the three forthcoming frames. The frame corresponding to the end of the movement was chosen after verifying that the marker displacement did not vary and/or reversed direction in the three successive frames. The time at which maximum grip aperture and peak velocity of grip aperture occurred were also calculated as a percentage of grasping time.

To test for possible differences across experimental conditions, a mixed analysis of variance (ANOVA) with “olfactory condition” (congruent, incongruent, control) and “target size” (small, large) as within-participant factors and “group” (aTBI, nTBI, control) as between-participant factor was performed for each of the considered dependent measures. Simple effects were used to explore the means of interest. In order to reduce the possibility of Type I error, when multiple comparisons were required, Bonferroni's corrections (α -level: $p < .05$) have been applied.

RESULTS

Table 2 reports mean values and the statistics relative to the considered variables. Among these variables, it was only the peak velocity of grip aperture that differed across conditions. For this measure, the ANOVA revealed a significant main effect of “dimension,” $F(1, 20) = 49.21, p < .001, \eta_p^2 = .71$, and the two-way interaction “olfactory condition by target size,” $F(2, 40) = 11.94, p < .001, \eta_p^2 = .37$. No effect of “group” was evident, $F(4, 40) = 0.87, p > .05, \eta_p^2 = .03$. As represented in Figure 3, aTBI patients sped up grip aperture when a “small” odor, rather than a “large” odor or no odor, preceded the presentation of a large to-be-grasped object ($p < .05$). Similarly, aTBI patients exposed to a “large” odor, rather than a “small” olfactory cue or no odor, slowed down the velocity of grip aperture when grasping for a small visual target ($p < .05$). A similar pattern of results emerged also for the nTBI and the control groups (Figure 3). Based on the odor anticipating the reach-to-grasp movement, all of the three groups showed an interference effect

TABLE 2
Means and standard deviations for the considered dependent measures for the traumatic brain injured patients and the healthy participants

Dependent variable (unit of measurement)	Olfactory condition	Target size	aTBI		nTBI		Controls		Statistical values
			Mean	SD	Mean	SD	Mean	SD	
Maximum grip aperture (ms)	Congruent	Small	681	90	681	90	703	66	$F(4, 40) = 2.18, p > .05$
		Large	570	66	704	66	616	49	
	Incongruent	Small	757	105	715	105	714	78	
		Large	575	82	645	82	618	60	
	Control	Small	693	72	704	72	611	53	
		Large	538	60	652	60	569	44	
Maximum grip aperture (mm)	Congruent	Small	113	4	111	4	107	3	$F(4, 40) = 2.65, p > .05$
		Large	64	3	66	3	61	2	
	Incongruent	Small	112	4	111	4	105	3	
		Large	66	3	70	3	62	2	
	Control	Small	112	4	110	4	106	3	
		Large	68	3	68	3	61	2	
Maximum grip aperture (%)	Congruent	Small	58	3	65	3	65	3	$F(4, 40) = 2.20, p > .05$
		Large	49	4	61	4	58	3	
	Incongruent	Small	61	4	67	4	65	3	
		Large	51	4	58	4	57	3	
	Control	Small	62	4	67	4	64	3	
		Large	49	4	58	4	55	3	
Peak velocity of grip aperture (ms)	Congruent	Small	282	43	319	43	306	32	$F(4, 40) = 0.04, p > .05$
		Large	207	58	285	58	245	43	
	Incongruent	Small	238	55	248	55	282	40	
		Large	345	65	393	65	364	48	
	Control	Small	282	41	399	41	297	31	
		Large	218	50	304	50	241	37	
Peak velocity of grip aperture (mm/s)*	Congruent	Small	427	48	381	48	364	35	$F(4, 40) = 11.94, p < .05$
		Large	296	32	249	32	205	24	
	Incongruent	Small	423	48	387	48	352	36	
		Large	273	37	261	37	213	27	
	Control	Small	428	46	365	46	390	34	
		Large	324	32	253	32	201	23	
Peak velocity of grip aperture (%)	Congruent	Small	25	4	30	4	30	3	$F(4, 40) = 2.02, p > .05$
		Large	19	5	25	5	26	4	
	Incongruent	Small	30	4	37	4	33	3	
		Large	21	4	23	4	28	3	
	Control	Small	26	3	37	3	31	2	
		Large	20	5	27	5	25	3	

Note. aTBI: anosmic traumatic brain injured patients; nTBI: normosmic/mildly microsmic traumatic brain injured patients; controls: neurologically healthy control participants. Statistical values refer to the two-way interaction of olfactory condition by dimension. Asterisk indicates the only significant dependent measure.

on the peak velocity of grip aperture. The comparison between congruent and no odor conditions for both the large and the small object did not reveal any facilitation effect ($p > .05$), except for the nTBI group when requested to act upon the large objects ($p < .05$).

DISCUSSION

The purpose of the present study was to evaluate the possible existence of lingering implicit odor processing in anosmic TBI patients. The present findings indicate that aTBI patients do show some form

of residual subliminal processing of olfactory stimuli. As for the normosmic/microsmic TBI patients and the neurologically healthy participants, aTBI participants show an interference effect at the level of the peak grip aperture velocity when presented with an odor incongruent with the size of the visual target. This occurred independently of the size of the to-be-grasped visual target. However, no facilitation effects emerged from the comparison of the congruent and the no odor conditions for any of the variables related to the grip phase. The data concerning the maximum grip aperture showed a trend compatible to what has been found for the

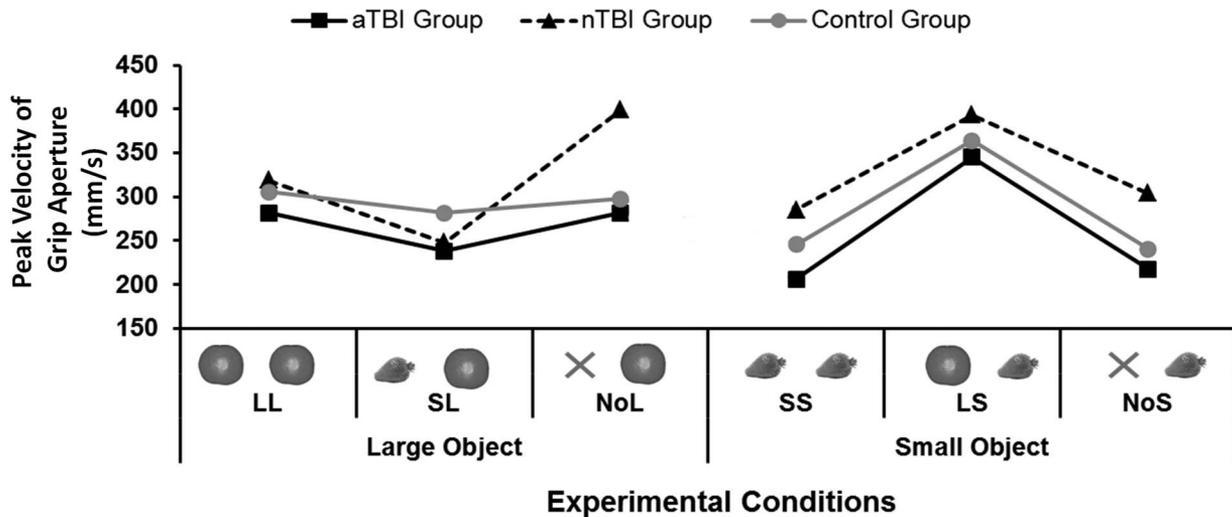


Figure 3. Lines represent the peak velocity of grip aperture expressed in mm/s for the anosmic traumatic brain injury (TBI) group (aTBI; black solid line), normosmic/microsmic TBI group (nTBI Group; black dashed line), and healthy participants (Control Group; grey solid line) for the six experimental conditions tested (from left to right: congruent, incongruent, no odor condition for the large and for the small targets, respectively). LL: congruent large condition; SS: congruent small condition; SL: incongruent large condition; LS: incongruent small condition; NoL: no odor large condition; NoS: no odor small condition.

peak of grip aperture velocity. Also, the analysis performed on this variable was very close to significance ($p < .054$). However, it is worth noting that both the peak grip aperture velocity and the maximum grip aperture are variables that provide indications on the manipulation phase of the reach-to-grasp movement. Moreover, they are interrelated parameters. The peak of grip aperture velocity is calculated as the time derivative of the maximum grip aperture (i.e., distance). Therefore, it includes the information regarding the maximum grip aperture, and, additionally, it puts this information in the temporal perspective of the movement. For this reason, it might be acknowledged that the velocity of maximum grip aperture is a kinematical parameter sensitive to size changes as the maximum grip aperture (Paulignan, Jeannerod, MacKenzie, & Marteniuk, 1991).

Altogether, the present findings seem to suggest that the anticipation of target size information via an odor cue has the potency to affect the motor control of the hand in these patients, revealing an actual implicit olfactory elaboration. This is a relevant finding given that TBI patients diagnosed with anosmia are thought to be completely unable to adequately react to odors.

Running parallel to the olfactory issue, the present work also provides novel insights into the parameterization of the reach-to-grasp movement in TBI patients, a population that have never been tested with this experimental paradigm. The results indicate that TBI patients shape grip aperture in accordance with the size of the object. With specific reference to olfaction, the findings

reported here confirm that in TBI patients, either anosmic or not, the perception of odors can modulate the manipulation phase of the reach-to-grasp movement as previously evident for healthy participants (Castiello et al., 2006; Tubaldi, Ansuini, Tirindelli, et al., 2008). Specifically, the occurrence of an interference effect reveals that the planning of the reach-to-grasp action is rooted in the irrelevant olfactory information preceding the sight of the to-be-grasped target. Put differently, the motor plan subliminally activated by the “size” of the incongruent odor leak into the motor plan specifically tailored to grasp the visual target. This parallel activation of two motor representations based on different structural properties, elicited by an olfactory cue incongruent to the visual target, well explains the differences evident at the kinematical level. When the “size” of the odor did match the size of the visual target, facilitation effects were expected. But, they did not emerge for any of the groups considered here. A possible explanation for this negative outcome might be that the peak velocity of grip aperture is not sufficiently fine-grained as to discriminate between the contribution of different sensory modalities conveying the equivalent information to accomplish the task goal. Alternatively, having two sensory systems signaling the very same structural information might contribute to the execution of a more stable action.

A possible explanation for the present findings might consider the existence of different and dissociable mechanisms responsible for olfactory processing. Olfactory deficits in TBI patients have

been mostly described in behavioral terms on the basis of odor recognition tests (Bonanni et al., 2006; De Kruijk et al., 2003; Fortin et al., 2010; Fujiwara et al., 2008; Geisler et al., 1999; Green et al., 2003; Roberts et al., 2010; Sandford et al., 2006; Sigurdardottir et al., 2010; Swann et al., 2006; Yousem et al., 1996). Only occasional attempts have been made to extend the evaluation of TBI olfactory abilities to odor discrimination and threshold (Haxel et al., 2008; Landis et al., 2010). Nevertheless, these kind of psychophysical tests require the integrity of some cognitive functions in order to efficiently complete the task (Olsson et al., 2002). That is, efficient verbal and memory skills are compulsory. However, these functions are usually compromised in people presenting head trauma outcomes (e.g., Jennet & Teasdale, 1981). Thus, it is not surprising that these patients fail when tested with classical explicit olfactory methods. Nevertheless, these kind of psychophysiological tests suggest that TBI patients might not require conscious recollection of olfactory stimuli, and therefore the integrity of structures devoted to explicit memory functions, supporting the evidence that both storage of and access to olfactory information might be automatic and implicit (e.g., Zucco, 2003). Support for this interpretation might come by the fact that anosmic participants, when asked to explicitly rate odors in terms of detectability, intensity, and familiarity, performed significantly worse than normosmic TBI patients and the healthy control participants. In this connection, it is worth remembering that implicit processing in TBI patients has been reported for other kind of stimuli such as faces (e.g., De Haan, Young, & Newcombe, 1987).

Moving to a neural level, which might be the cerebral substrates regulating implicit odor processing? Whenever undamaged, the piriform or the entorhinal cortex might act as possible candidates, given that they have been previously shown to be activated during the passive presentation of olfactory stimuli (Savic, Gulyas, Larsson, & Roland, 2000). Neuropsychological evidence also suggests that lesions at the level of the right temporal lobe may produce odor (as well as face) agnosia by preventing familiar information from accessing the semantic association necessary to consciously identify the odors (Mendez & Ghajarnia, 2001).

As a subsequent (or independent) step, the amygdala might be recruited. The amygdala is a region embedded within the rhinencephalon (Bargmann & Schädé, 1963), it is physically close to and widely interconnected with the primary olfactory brain areas (Price, 1990), and it is has an active role in emotional regulation (LeDoux,

2000). For these reasons, it might mediate olfactory information—especially those related to survival decisions (Koenig, Bourron, & Royet, 2000)—which appears to be detached from higher mental functions. Support to this contention comes also from the fact that olfaction is the only sense that bypasses first-relay/direct connections with the thalamus, a structure apparently involved in conscious processes (Plailly, Howard, Gitelman, & Gottfried, 2008).

The connections between the amygdala and the orbitofrontal cortex (OFC) suggest that this latter region also contributes to subliminal olfactory perception (Price, 1990). Moreover, its role in multisensory integration of stimuli serving the guidance of goal-directed behavior well fits with the implicit nature of the odor processing described here. These two areas might work in team as the amygdala may encode the significance of cues, and subsequently the OFC might work as a centre for multisensory appraisal, guiding functional goal-directed behaviors rooted on information accessed through various interconnected structures, amygdala in primis (Schoenbaum, Chiba, & Gallagher, 1998).

This hypothesis seems to be supported by the interference effects found in the TBI patients when the visual and the olfactory stimuli did not match. Evidence from neuroimaging (Gottfried & Dolan, 2003; Österbauer et al., 2005) and neurophysiological studies (Grigor, 1995; Grigor, Van Toller, Behan, & Richardson, 1999; Rolls & Baylis, 1994; Sarfarazi, Cave, Richardson, Behan, & Sedgwick, 1999; Stein & Meredith, 1990) indicate that the manipulation of the level of congruency between visual and olfactory stimuli correlates with a compatible modulation of the neural activity of OFC.

In order to fully account for the present results, the visuo-olfactory representation formed within the OFC on the basis of amygdala odor inputs needs to be translated in motor terms. In this respect, direct connection between OFC and motor areas involved in arm–hand movement control has been traced (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Morecraft & Van Hoesen, 1993). In the light of the commonly accepted homology between cerebral regions underlying reach-to-grasp movements in monkeys and humans (for review, see Castiello, 2005), it is tempting to posit that the corticocortical connections between OFC and motor areas (e.g., Bates & Goldman-Rakic, 1993) can justify the multisensory modulation of olfactory–visual information on motor behavior in general and, specifically, on grasping actions (Rossi et al., 2008).

Given the dispersed localization of the brain areas possibly involved in the performance of the present visuo-olfactory motor task and their tight interconnections, it is not surprising that TBI patients present some residual implicit olfactory abilities. Although no definite conclusions can be drawn from the present findings, it is tempting to speculate that lesions compatible with the performance of the task at hand are unlikely to simultaneously involve all the regions involved in the implicit olfactory processing network. As a result, some residual implicit olfactory abilities can be preserved even in anosmic TBI patients.

To sum up, TBI patients' prehensile movements may be affected by the chain of neural events beginning with implicit odorant encoding occurring at the amygdala level, continuing within OFC, and, finally, reaching central motor areas. This is the hypothesized mechanisms at the basis of the preserved implicit olfactory processing in TBI patients.

However, before drawing definite conclusions on this issue, some limitations of the present study should be outlined. Most importantly, it would be of help increasing the sample size and equalizing the number of the female and male participants. For the sake of homogeneity, we were forced to exclude a number of potential participants. As an example, in some cases, the severity of the impairment did not allow for sufficient compliance to task instructions. In fact, some patients presenting frontal and temporal lobe lesions showed difficulties in planning and executing chains of tasks, such as that described in the present study. As another example, some of the patients tested became easily tired and, therefore, did not complete the experimental session and quit the evaluation.

Furthermore, future research is needed in order to fully disentangle the issue of olfactory processing in TBI patients. In the first instance, it would be interesting to administer these patients with odors conveying biologically relevant information. This might help to better understand how TBI patients deal with social chemosignals as to facilitate adequate social skills. This is an aspect that is frequently affected in these patients. A deeper comprehension of the mechanisms regulating olfactory processing might be useful in developing new rehabilitation strategies. As an example, the present paradigm might be used to train crossmodal attention, an ability that allows us to adaptively navigate the environment. As another example, in the light of the strict link between neural structures regulating emotions and olfactory stimuli, odors might serve

to rehearse autobiographical events, contributing to personal orientation and an improved quality of life.

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