Diminished Neural and Cognitive Responses to Facial Expressions of Disgust in Patients with Psoriasis: A Functional Magnetic Resonance Imaging Study

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Psoriasis produces significant psychosocial disability; however, little is understood about the neurocognitive mechanisms that mediate the adverse consequences of the social stigma associated with visible skin lesions, such as disgusted facial expressions of others. Both the feeling of disgust and the observation of disgust in others are known to activate the insula cortex. We investigated whether the social impact of psoriasis is associated with altered cognitive processing of disgust using (i) a covert recognition of faces task conducted using functional magnetic resonance imaging (fMRI) and (ii) the facial expression recognition task (FERT), a decision-making task, conducted outside the scanner to assess the ability to recognize overtly different intensities of disgust. Thirteen right-handed male patients with psoriasis and 13 age-matched male controls were included. In the fMRI study, psoriasis patients had significantly ($P<0.005$) smaller signal responses to disgusted faces in the bilateral insular cortex compared with healthy controls. These data were corroborated by FERT, in that patients were less able than controls to identify all intensities of disgust tested. We hypothesize that patients with psoriasis, in this case male patients, develop a coping mechanism to protect them from stressful emotional responses by blocking the processing of disgusted facial expressions.

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INTRODUCTION

Psoriasis has a significant negative impact on the physical and psychosocial well-being of those it afflicts comparable with that of patients with cancer, heart disease, or diabetes mellitus (Rapp *et al.*, 1999).

The ''brain–skin axis'' is emerging as a useful concept in understanding how skin disease produces psychosocial disability and how stressful life events may exacerbate inflammatory skin disease (Bremner *et al.*, 2005; Paus *et al.*, 2006; reviewed in Sternberg, 2006). However, little is known about the neurocognitive mechanisms that mediate the adverse social and psychological consequences of the stigma and humiliation associated with visible skin lesions (Wahl *et al.*, 2002; reviewed in De Korte *et al.*, 2004). Our earlier work has shown that psoriasis patients, relative to controls, commonly believe that they will be evaluated solely on the basis of their skin and they use anticipatory and avoidance social coping behaviors (Fortune *et al.*, 1997, 2003). We hypothesize that a key cue is the perception of subtle degrees of disgust in the expression of others. It is well known that different facial emotions evoke overlapping patterns of neural activity in the ventral visual processing stream, in the amygdala, and the ventral frontal cortex, with additional areas specifically engaged by particular emotions (Anderson *et al.*, 2007). Expressions of disgust are notable in activating the insula cortex, part of the interoceptive gustatory pathway (Phillips *et al.*, 1997).

Here we investigate whether the social impact of psoriasis is associated with altered cognitive processing of the expression of disgust. In this preliminary study, we focused on male patients only, as responses to facial emotions may be confounded by gender in a mixed group, making interpretation difficult in a small sample. We used two methodologies: (i) a task to assess covert recognition of faces conducted in conjunction with functional magnetic resonance imaging (fMRI) to determine the blood oxygenation level-dependent

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Abbreviations: BOLD, blood oxygenation level-dependent; 95% CI, 95% confidence interval; FERT, facial expression recognition task; fMRI, functional magnetic resonance imaging; HADS, Hospital Anxiety and Depression Scale; OR, odds ratio; PASI, Psoriasis Area and Severity Index; VAS, visual analog scale

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(BOLD) response in the insula and (ii) the facial expression recognition task (FERT; Harmer *et al.*, 2001), a decision-making task, conducted outside the scanner to assess the ability to recognize overtly, facial expressions of disgust at different intensities.

RESULTS

Participant characteristics

Thirteen right-handed male patients (mean age: 35.8 ± 2.3 years; range: 18–45) with a dermatologist-confirmed diagnosis of chronic plaque psoriasis (mean Psoriasis Area and Severity Index (PASI): 5.3 ± 3.6; range: 1.1–12.2) and 13 age-matched right-handed male controls (mean age: 31.2 ± 2.1 years; range: 19–43) with no history of skin disease participated in the study between July 2006 and August 2007. Patients were recruited irrespective of current psoriasis treatment that included topical treatment ($n=4$), methotrexate ($n=5$), acitretin ($n=1$), infliximab ($n=1$), and no treatment ($n=2$). The psoriasis and control groups were matched for age using a 5-year age band on either side of the matched patient and the groups were well balanced.

Psychometric data

Fear of negative evaluation. In order to discriminate between patients with social anxiety and both non-patient controls and patients with other anxiety disorders, potential volunteers who scored >20 out of a total of 30 ($n=5$) were not included in the study (Watson and Friend, 1969; Rodebaugh *et al.*, 2004). We observed similar mean scores in both controls (8.3 ± 1.4) and patients with psoriasis (8.8 ± 1.7).

Hospital anxiety and depression scale. Participants did not have a psychiatric diagnosis and scored below cutoffs for clinical anxiety and depression.

The mean Hospital Anxiety and Depression Scale (HADS) anxiety score was 5.15 ± 0.77 (range: 0–11) for the control group and 7.08 ± 0.91 (range: 2–14) for the psoriasis group. Although there was a trend of increased anxiety scores in the patient group, there was no significant statistical difference between the two groups ($P=0.12$; 95% confidence interval (95% CI): −4.38 to 0.53).

The mean HADS depression score was 2.77 ± 0.66 (range: 0–8) for the control group and 3.69 ± 0.60 (range: 0–7) for the psoriasis group. Similarly, there was no statistically significant difference between the groups ($P=0.32$; 95% CI: −2.78 to 0.92).

Visual analog scale. Participants used a linear visual analog scale (VAS) to record the amount of anxiety experienced at baseline and post-testing in the scanner. This scale ranged from 0 (''not at all'') to 100 (''very much''). There was a significant ($P=0.03$; 95% CI: 0.6–14.1) reduction of mean VAS score from baseline in controls. In contrast, a non-significant ($P=0.09$; 95% CI: −1.6 to 18.5) reduction of mean VAS score from baseline in the patients with psoriasis was observed. The difference between the groups in terms of mean change in VAS scores was not significant (Table 1). These data suggest that anxiety prompted by anticipation was allayed once the study was completed.

fMRI data

Patients have diminished response to facial expressions of disgust. The pattern of BOLD responses to disgusted compared with neutral faces in patients and controls combined was consistent with earlier studies (Anderson *et al.*, 2007; reviewed in Posamentier and Abdi, 2003). Bilateral responses occurred in the inferior frontal cortex; insula, temporal and occipital cortices; and the putamen (Table 2). The effect of disgusted facial expressions, as compared with neutral facial expressions, across both patients and controls produced more widespread activation than fearful facial expressions (Tables 2 and 3).

Our key hypothesis was with regard to the differences between patients and controls. Between-group comparisons showed significantly attenuated BOLD response in the bilateral insula of psoriasis patients compared with that of controls (Table 2; Figure 1).

Patients and controls have similar response to facial expressions of fear. The main effect of fearful faces compared with neutral faces across both groups bilaterally activated amygdalae and lateral orbitofrontal cortex, and temporal and occipital cortices. There was no significant difference between the two groups, suggesting that the difference associated with disgust is specific to that emotion.

FERT. These fMRI data were corroborated by FERT, which showed that patients are less able than controls (odds ratio, (95% CI): 0.4, (0.2–0.81); $P=0.017$) to identify all intensities of disgust tested (Figure 2). There was no intergroup difference in terms of processing of fear (0.98, (0.59–1.63); $P=0.93$) or sadness (1.15, (0.6–2.20); $P=0.67$).

Table 1. VAS scores recorded by controls (n=12) and patients with psoriasis (n=12)

	Baseline[1]	Post-fMRI[1]	Mean change (baseline–post-fMRI)[1]	Difference: controls–psoriasis patients (95% CI)[2]	*P*-value[3]
Controls	17.4 ± 2.5[4]	11 ± 3.1[4]	7.4 ± 3.0	1.1 (−10.6 to 12.7)	0.9
Psoriasis	19.2 ± 4.6[4]	9.9 ± 3.3[4]	8.4 ± 4.6		

CI, confidence interval; fMRI, functional magnetic resonance imaging; VAS, visual analog scale.
[1]Mean ± SEM.
[2]Difference between controls and patients with psoriasis in terms of change in mean VAS scores from baseline.
[3]*P*-values were obtained using an independent two-sided *t*-test (equal variances not assumed).
[4]n varies from $n=11$ to $n=12$ due to a few missing data values.

Table 2. Maximally activated voxels in areas in which significant evoked activity was related to covert recognition of disgusted faces blocks compared with neutral faces blocks

Main effect (controls + patients)								Controls–patients			
					MNI coordinates (mm)				MNI coordinates (mm)		
Region	**BA**	**LR**	k_E	***Z*-score**	***x***	***y***	***z***	***Z*-score**	***x***	***y***	***z***
Inferior frontal gyrus	47	L	**96**	**4.21**	**−47**	**34**	**−11**				
		R	**93**	**4.38**	**52**	**31**	**−7**				
Insula	13	L						2.62	−52	4	−7
		R						3.55	38	11	−18
Temporal gyrus	21	L	**33**	**4.15**	**−61**	**−11**	**−14**				
		R	**62**	**3.84**	**61**	**−7**	**−21**				
		L	16	3.74	−67	−34	−4				
		R	115	3.84	58	−27	−7				
	38	L	52	4.01	−40	5	−21				
		R	26	3.94	40	9	−25				
	37	L	59	3.85	−58	−67	0				
		R	**114**	**4.05**	**52**	**−56**	**−11**				
Precuneus	7	L/R	62	3.67	7	−65	32				
Fusiform gyrus	19	L	10	3.39	−47	−67	−18				
		R	**65**	**4.01**	**47**	**−70**	**−14**				
	37	R	**32**	**4.06**	**47**	**−45**	**−25**				
Occipital gyrus	18	L	**60**	**4.20**	**−36**	**−92**	**−11**				
		R	**178**	**4.21**	**31**	**−97**	**−4**				
Amygdala	34	L	**39**	**3.87**	**−23**	**0**	**−21**				
		R	**20**	**3.59**	**23**	**4**	**−18**				
Caudate	—	L	**17**	**3.50**	**−7**	**7**	**0**				
Putamen	—	L	**52**	**3.19**	**−18**	**14**	**0**				
		R	**96**	**3.35**	**22**	**7**	**−4**				

BA, Brodmann area; L, left; MNI, Montreal Neurological Institute; R, right.
The statistical map height thresholds were $P<0.001$ for the main effect and $P<0.005$ for the control–patients comparison. Both maps used an extent threshold of $k_E=10$.
Unbolded values do not survive small volume correction for multiple comparisons at P (Family-Wise Error; FWE) <0.05 but are included because the activation is bilateral.

DISCUSSION

To the best of our knowledge, this is the first study to use fMRI to investigate the effect of aversive facial expressions on patients with psoriasis. We found significantly reduced response in the insula cortex of patients compared with controls when observing disgusted faces. This was accompanied by a behavioral deficit in detecting disgusted emotion as measured by the FERT task. These effects were specific to disgust; patients did not differ from controls in their brain response to or recognition of fearful faces.

In both controls and patients, responses to disgusted and fearful faces were associated with BOLD signal responses in a network of brain regions consistent with other reports in the literature (reviewed in Posamentier and Abdi, 2003). The magnitudes of signal changes we observed were also consistent with earlier studies in controls (Del-Ben *et al.*, 2005) and in other patient groups (Surguladze *et al.*, 2005). Consistent with the literature, the insula response was associated with response to disgust but not to fear. The insula has therefore been postulated as a key region of the

Table 3. Maximally activated voxels in areas in which significant evoked activity was related to the covert recognition of fearful faces blocks compared with the recognition of neutral faces blocks

Main effect (controls + patients)

				MNI coordinates (mm)		
Region	**BA**	**LR**	***Z*-score**	***x***	***y***	***z***
Lateral orbitofrontal cortex	47	L	3.97	−40	25	−18
		R	3.27	50	32	−14
Fusiform gyrus	37	L	3.84	−36	−86	−14
		R	4.61	22	−79	−18
Temporal pole	38	L	3.79	−32	16	−32
		R	3.37	38	22	−28
Occipital cortex	18	L	4.37	−27	−94	0
		R	3.97	40	−90	4
Amygdala		L	3.62	−18	−5	−25
		R	**2.76**	**23**	**2**	**−18**

BA, Brodmann area; L, left; MNI, Montreal Neurological Institute; R, right. Statistical maps were thresholded at $P<0.001$. Bilateral observations reported at a lower significance if observed.
[1]Bold values indicate below threshold but are included because the activation appears bilateral.

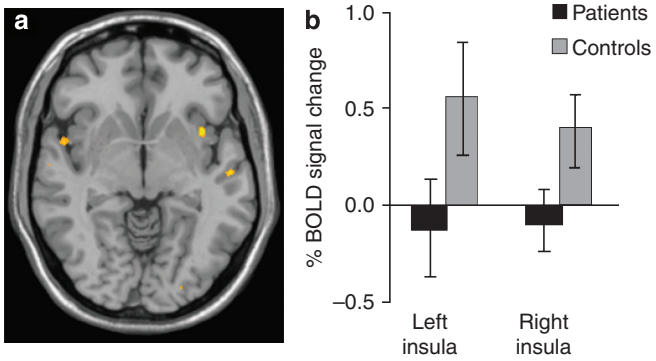

Figure 1. Reduction of BOLD signal in bilateral insula of psoriasis patients for processing of disgust. Thirteen right-handed male patients with chronic plaque psoriasis and 13 age-matched right-handed male controls were recruited to the study. All participants were tested using a covert recognition of faces task performed while Philips 3.0 Tesla MR images were acquired. Participants were presented with A, neutral; B, 100% disgusted; and C, 100% fearful facial expressions of emotion in a traditional block design, i.e., ABACABACABAC. The total task duration was 6 minutes and 45 seconds. Participants were instructed to identify whether the faces were male or female and make a button box response accordingly. (**a**) Bilateral insula activation in psoriasis patients is depicted. (**b**) The results are shown as percentage BOLD signal change per group derived from random effects analysis, using a two-sample *t*-test, for disgust. Error bars reflect 90% confidence interval. Psoriasis patients had significantly ($P<0.005$) smaller BOLD signal responses as compared with healthy controls.

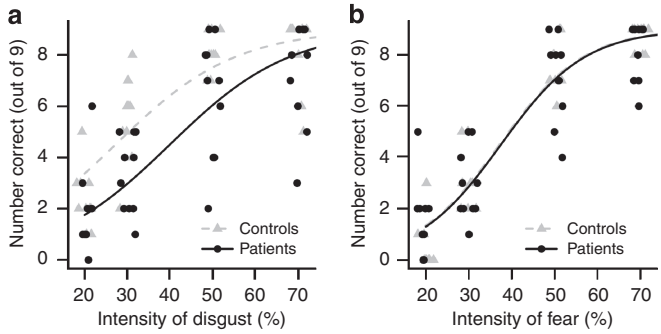

Figure 2. The odds of controls detecting facial expressions of disgust across all disgust intensities is twice as likely than for patients with psoriasis. The facial expression recognition Task (FERT), a decision-making task, conducted outside the scanner was used to assess the ability to recognize overtly, facial expressions of disgust at different intensities. Results are shown as numbers of correct responses as a function of intensity of disgust (**a**) and fear (**b**). Points are slightly offset to improve clarity (levels were 20, 30, 50, and 70%). The lines show the fitted mixed logistic regression fits to the data in each group. (**a**) Psoriasis patients showed fewer correct responses across all disgust intensities. (**b**) The difference between the groups in terms of processing facial expressions of fear is very small and the lines are almost co-incident.

brain for processing disgust, responding to both disgusted expressions in others and to pictures eliciting disgust in subjects (Wicker *et al.*, 2003).

Critically, we observed a significant attenuation of the insula response to disgust in psoriasis patients, in the absence of any significant differences in fear response. One possible explanation of this is that psoriasis patients develop a coping mechanism to protect them from stressful emotional responses by blocking the processing of disgusted facial expressions encountered in others. Some support for this hypothesis comes from the FERT task results, which show that the psoriasis patients have impaired ability to recognize disgust, but not other negative emotions.

There are a number of possible underlying mechanisms of this effect. The insula has been implicated in stigmatization judgments (Krendl *et al.*, 2006), which may relate to the stigmatization experiences of psoriasis patients (Wahl *et al.*, 2002; De Korte *et al.*, 2004).

The observed results may also be related to empathy. fMRI studies have shown that the observation of pain in others is mediated by the insula as well as by the anterior cingulate cortex, and these responses are attributed to empathy (Chakrabarti *et al.*, 2006; de Vignemont and Singer, 2006). It is therefore possible that the reduced insula response in psoriasis patients is associated with reduced empathy for disgust, perhaps resulting from desensitization.

However, psoriasis patients show normal responses to both disgust and fear in the inferior frontal gyrus, temporal gyrus and amygdala, which are other areas that play key roles in social cognition and empathy (Iacoboni and Dapretto, 2006). An impairment in empathy would probably be associated with abnormal functional responses in these regions as well as in the amygdala, although it is possible

that a more explicit test of empathy would be required to detect subtle abnormalities.

In terms of PASI scores, patients with psoriasis were categorized as having mild or moderate chronic plaque psoriasis. Despite the limitations of the PASI (Marks *et al.*, 1989; Ashcroft *et al.*, 1999; Feldman and Krueger, 2005), these scores give an indication that our sample of patients with psoriasis was not confined to those with the most severe, treatment-resistant form of disease (PASI > 20). For the purpose of this study, we did not focus on or sub-stratify the group into those with psoriasis on exposed versus nonexposed areas, as we wanted to determine whether there was a difference *per se* between the patients with psoriasis and healthy volunteers. Furthermore, we did not observe a correlation between PASI score and neural response in the pre-hypothesized areas.

Consistent with earlier studies, socially anxious individuals were excluded because it is known that anxiety may influence processing of facial expressions of emotion in terms of reaction time to stimuli and brain regions activated (Phillips *et al.*, 1997; Del-Ben *et al.*, 2005). However, there was a nonsignificant trend for higher HADS anxiety and depression scores among patients with psoriasis as compared with controls. Our small sample has limited power to show statistical significance and it is therefore possible that the patients may have sub-syndromal psychological morbidity. Furthermore, we recruited male patients, and it is possible that psychological morbidity is enhanced in female patients and this may be associated with different patterns of brain response to emotional faces. Further research is needed to clarify this issue.

In conclusion, the specific insula dysfunction observed in this study provides a biologically plausible basis for observed psychological associations of psoriasis. This first application of fMRI to abnormalities of emotional processing in chronic skin disease suggests that it may provide previously unreported insights into the brain–skin axis. Such insights could generate new strategies for managing stigmatizing skin diseases.

MATERIALS AND METHODS

Clinical protocol

The study protocol was approved by an independent local research ethics committee (Salford and Trafford, Manchester, UK) and the Declaration of Helsinki protocols were followed.

Volunteers were recruited and interviewed over a 13-month period from July 2006 to August 2007. The study was performed in healthy volunteers, who responded to local advertisement at The University of Manchester and Salford Royal Hospital, and patients with psoriasis who attend a specialist Psoriasis Clinic (Salford Royal Hospital, Manchester, UK). All volunteers had to comply with inclusion and exclusion criteria that, briefly, included (i) age between 18 and 45 years, (ii) right-handed, (iii) male, (iv) nonsocially anxious, (v) not taking psychotropic medication, (vi) no contraindications to fMRI scanning (below), and (vii) presented no history of severe or enduring mental or neurological illness.

All prospective participants were screened for social anxiety, using the fear of negative evaluation, preenrollment to the study (below).

On the day of testing, following written, witnessed, informed consent, all participants had a clinical assessment that included a full medical history, to evaluate suitability for undergoing an fMRI scan, and skin examination. Contraindications to having a brain scan included (i) the presence of a cardiac pacemaker, (ii) previous cardiac or brain surgery, (iii) a history of a penetrating eye injury involving metal, and (iv) any surgery within 2 months of the study participation.

Participants were instructed how to prosecute the task and underwent ~7 minutes of testing within the MR scanner followed by a 6-minute structural brain scan. Thereafter, participants completed a VAS to record level of anxiety experienced by undergoing the fMRI scan.

Imaging experimental design

The covert recognition of faces task was performed while Philips (Eindhoven, Holland) 3.0 Tesla MR brain images were acquired (TR (repetition time) = 5 seconds, 3.5 mm thickness with an in-plane resolution of 1.8 × 1.8 mm, TE (echo time) = 37 mseconds). Participants were presented with A, neutral; B, 100% disgusted; and C, 100% fearful facial expressions of emotion (Ekman and Friesen, 1976) in a traditional block design, that is, ABACABACABAC. These emotions had been selected from the full set of face emotions on the basis of their signaling different negative emotions related to immediate aversive environmental situations (Del-Ben *et al.*, 2005). The total task duration was 6 minutes and 45 seconds, each block lasted 33.75 seconds and comprised nine pictures of the appropriate emotion, each presented for 3 seconds with an interstimulus interval of 0.75 seconds. Participants were instructed to identify whether the faces were male or female (Phillips *et al.*, 1997). They were neither asked to examine the facial expression nor to make a decision on the emotions expressed. The task was back projected on to a screen visible to the participant through two mirrors attached to the head coil. Responses were given through a fiber-optic button box, using the right hand. A T_1-weighted structural image was also acquired for each participant to exclude any structural abnormalities. No abnormalities were reported for any of the 26 participants.

FERT

The FERT, adapted from Harmer *et al.*, tested four intensities of disgust (20, 30, 50, and 70%). Fear and sadness were included as aversive controls. In the main task, 108 stimuli (9 actors × 3 facial expressions × 4 intensities) were each presented for 0.5 seconds (interstimulus interval = 4 seconds).

Psychometric assessments

Fear of negative evaluation scale. This 30-item scale provides an assessment of worries and fears of rejection. It has been shown to discriminate between patients with social anxiety and both non-patient controls and patients with other anxiety disorders (Rodebaugh *et al.*, 2004). Respondents are instructed to tick ''true'' or ''false'' for each question. Each item is scored on a 0–1 scale, 1 being assigned to a response that indicates anxiety. A maximum total score of 30 may be achieved. Potential volunteers who scored >20 were not included in the study.

HADS. The HADS was originally developed to detect anxiety and depression among patients with physical illnesses, and the

depression scale is constructed to minimize the effect of somatic disorders in the identification of depression (Zigmond and Snaith, 1983). Patients are requested to tick the response to the statement most relevant to them. The 14 items, each being scored on a 0- to 3-point scale, measure degrees of anxiety (seven items) and depression (seven items). The two subscale scores thus range from 0 to 21. A score of 8–10 suggests a possible psychological disorder, whereas scores of 11–21 indicates a probable psychological disorder on each of the subscales (Richards *et al.*, 2004).

Clinical assessment

PASI. PASI is a widely used measure of physical psoriasis severity. It is a composite score ranging from 0 to a theoretical maximum of 72 (Fredriksson and Pettersson, 1978). However, a composite PASI score of $\leqslant 10$ is, by convention, considered to be mild disease; PASI score between 10 and 20 would be described as moderate disease; and a PASI score of >20 is regarded as severe disease (Feldman and Krueger, 2005).

Data handling and statistical analysis

Imaging analysis. Imaging data were analyzed using Statistical Parametric Mapping (SPM5, The Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm), with a random effects model. Images were realigned to correct for motion artifacts using the first scan as a reference and normalized into the Talairach and Tournoux stereotactic space using Montreal Neurological Institute templates. The images were then smoothed. After this spatial preprocessing, first-level analysis was carried out on each participant to generate a single mean image corresponding to each aversive face block minus the neutral face block. Motor responses are matched in the experimental conditions and neuronal responses to button presses are therefore subtracted out of the analysis. The mean images for each participant were then combined in a second-level, random effects analysis, using a two-sample *t*-test for each emotion to investigate the main effect of the aversive emotion versus neutral regardless of group as well as of the regional BOLD response differences between the two groups.

Statistical maps were thresholded at $P<0.01$ uncorrected with a cluster size of 10 voxels, and voxels with $P<0.001$ uncorrected (*Z*-score >3.09) were reported. When bilateral activations were seen, lower levels of significance are reported.

Psychometric and VAS analysis. The statistical significance of differences of psychometric (fear of negative evaluation, HADS) and VAS scores between controls and patients was evaluated using the independent *t*-test (SPSS Software, SPSS, Chicago, IL).

FERT analysis. A mixed logistic model was fitted to the number of correct responses, treating these as binomial outcomes, with a random effect to allow for variability between participants (R Development Core Team Software, Vienna, Austria). The results are presented as odds ratios for the difference between groups and plots of the fixed effects. Significance is determined using likelihood ratio tests.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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