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| Journal: | *Social Neuroscience* |
| Manuscript ID: | SNS-CO 17.14.R1 |
| Manuscript Type: | Fast-Tracked Brief Report |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | Cardona, Juan; Institute of Cognitive Neurology,<br>Sinay, Vladimiro; Institute of Cognitive Neurology,<br>Amoruso, Lucia; Institute of Cognitive Neurology,<br>Hesse, Eugenia; Institute of Cognitive Neurology,<br>Manes, Facundo; Institute of Cognitive Neurology,<br>Agustín, Ibáñez; INECO, |
| Keywords: | Emotion recognition, NMO, executive functions, negative emotion networks |
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# The impact of neuromyelitis optica on the recognition emotional facial expressions: A preliminary report

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**Running head:** Emotional Facial Expressions in NMO

Words: 2575

**Acknowledgements**

This work was partially supported by grants from CONICYT/FONDECYT Regular (1130920 and 1140114), FONCyT-PICT 2012-0412 and FONCyT-PICT 2012-1309, CONICET and INECO Foundation. Any opinions, findings, conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of those grants.

## Abstract

Although neuromyelitis optica (NMO) is classically recognized as an affectation of optic nerves and spinal cord, recent reports have shown brain atrophy and cognitive dysfunction in this condition. Importantly, emotion-related brain regions appear to be impaired in NMO. However, no studies of NMO' emotional processing have been published. The goal of the current study was to investigate facial emotion recognition in 10 patients with NMO and 10 healthy controls by controlling for relevant cognitive factors.

Consistent with previous reports, NMO patients performed poorly across cognitive domains (divided attention, working memory and information processing speed). Our findings further evidence the relative inability of NMO patients to recognize negative emotions (disgust, anger, and fear), in comparison to controls; with these deficits not explained by other cognitive impairments.

Results provide the first evidence that NMO may impair the ability to recognize negative emotions. These impairments appear to be related to possible damage in brain regions underling emotional networks, including the anterior cingulate cortex, amygdala and medial prefrontal cortex. Findings increased both our understanding of NMO's cognitive impairment, and the neural networks underlying negative emotions.


Keywords: emotion recognition, NMO, executive functions, negative emotion networks

The interrelationship between brain involvement and cognitive processing in neuromyelitis optica (NMO) is an emerging field of research (Blanc et al., 2008; Blanc et al., 2012; He et al., 2011). Recently, neuroimaging studies have shown neuroanatomical (Blanc et al., 2012; Pittock et al., 2006) and functional abnormalities (Liu et al., 2011) in NMO. However, relatively little is known about the presence of cognitive, emotional and behavioral disturbances in patients with NMO.

NMO, also known as Devic's disease, is an inflammatory demyelinating disorder of the central nervous system (CNS) that mainly affects the optic nerves and white matter tracts in the spinal cord (Wingerchuk, Lennon, Lucchinetti, Pittock, & Weinshenker, 2007). The presence of the serum NMO immunoglobulin G (NMO-IgG) distinguishes NMO from other demyelinating diseases (Lennon et al., 2004; Weinshenker, Wingerchuk, Pittock, Lucchinetti, & Lennon, 2006). NMO-IgG binds selectively to aquaporin 4 (AQP4), the predominant water channel in the brain (Amiry-Moghaddam & Ottersen, 2003; Jung et al., 1994).

Neuroimaging studies have identified cortical-subcortical impairment in structures such as corpus callosum, insula, anterior cingulate (ACC), superior temporal gyrus and prefrontal cortex (He et al., 2011),as well as atrophy of white matter tracts that connect frontal, temporal and parietal regions, in the pathophysiology of NMO (Blanc et al., 2012). Cerebral regions affected in NMO appear to be involved in sensory, affective and cognitive processing. Researchers have begun to investigate neuropsychological performance in patients with NMO and revealed impairment in basic cognitive domains, including

learning-related activity, information-processing speed, divided attention and some deficits in executive dysfunction (Blanc et al., 2008; Blanc et al., 2012; He et al., 2011).

Importantly, the emotional brain network (Kennedy & Adolphs, 2012) (consisting of the ACC, insula and medial prefrontal cortex) seems to be affected in NMO and may possibly play a role in the recognition of facial expressions (Kennedy & Adolphs, 2012). However, the relationship between brain alterations in NMO and emotional processing remains unclear.

Given results showing that several emotion-related brain regions are involved in NMO, the goal of the current experiment was to investigate facial emotion processing at the behavioral level on patients with NMO. Preliminary findings suggest the presence of an additional symptom on NMO, which may improve diagnosis and treatment, as well as increase our understanding of the neural substrates of cognitive and emotional processes.

## MATERIALS AND METHODS

NMO group and controls: 10 patients with NMO and 10 healthy subjects were included in this study. The control group (CG) was matched to the NMO patients for age, sex and education.

NMO patients were diagnosed according to the recently revised diagnostic criteria proposed by Wingerchuk et al.(2006): optic neuritis, myelitis and the presence of at least two of the following three additional characteristics: 1) brain MRI results negative or non nondiagnostic for multiple sclerosis (MS) at onset, 2) MRI evidence of a spinal cord T2 lesion of three or more vertebral segments, and 3) a serological test result positive for NMO-IgG

Neurological and physical impairment in NMO patients was evaluated using the Expanded Disability Status Scale (EDSS). Only patients with bilateral upper limb weakness who did not present severe disabilities (mean EDSS score 2.25±1.01) were included in the study. None of the subjects had a severe visual impairment, history of alcohol abuse, or psychiatric or neurological disorder other than NMO (see table 1). Subjects read and signed a consent form in agreement with the Declaration of Helsinki before participating in the study. The ethical committee of the Institute of Cognitive Neurology approved the study.

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Table 1.

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NEUROPSYCHOLOGICAL ASSESSMENT

All participants underwent an extended evaluation including dementia measures and neuropsychological assessment of executive functions (see supplementary data 1 for additional details)

THE EMOTIONAL MORPHING TASK

Emotional morphing is a facial expression recognition task featuring 6 basic emotions (happiness, sadness, fear, surprise, anger and disgust; see figure 1a) taken from a series of pictures depicting various emotions (Ekman & Friesen, 1976). Dynamic face presentation, rather than static pictures, allows for more sensitive emotion discrimination and has been utilized in this study (see figures S1 in supplementary data). The pictures were morphed

between each prototype emotion and a neutral state (Young et al., 1997). Facial morphing was achieved by taking a variable percentage of the shape and texture differences between the two standard images, 0% (neutral) and 100% (full emotion), in 5% steps (500 ms for each image). The 48 morphed facial stimuli were randomly presented on a computer screen until the subject indicated a response on the keyboard. Participants were asked to respond as soon as they recognized the facial expression, and then to identify the facial expression from a forced-choice list of six options. This task measures the accuracy of emotion recognition and reaction times (RTs).

To control for the influence of cognitive dysfunction (e.g., executive functions) on facial emotions recognition tasks, we applied an analysis of covariance (ANCOVA) test adjusted for all neuropsychological scores.

## RESULTS

Regarding neuropsychological performance of patients with NMO, we replicated previous reports showing deficits in divided attention, working memory and information processing speed (Blanc et al., 2008). Additionally, we found systematic deficits in verbal inhibitory control (a summary of descriptive statistics and comparison between groups are provided in table S1 in supplementary data 2).

Significant differences in the accurate recognition of the six categories of emotion were observed, $F$ (5, 90) = 3.72, $p$ < .05. Post-hoc analysis (*Tukey HSD, MS* = .01, *df* = 107.98)

revealed reduced accuracy in NMO patients for emotions of disgust, $p$ = .007, anger, $p$ = 0.004, and fear, $p$ = 0.02, compared with controls (figure 1b).

Regarding the average RTs, the NMO group exhibited speeds [M=8075.26 ms, SD = 1514.25] equivalent to the control group [M=7404.05 ms, SD=715.58] [F(1,18) = 1.60, p=0.22] (figure 1c, see also table S2 in Supplementary data 3). Additionally, no significant covariation was found between the neuropsychological scores and the emotion recognition task.

Figure 1.

**DISCUSSION**

This preliminary study investigated cognitive functioning in patients with NMO, with a particular focus on facial expression processing. Our findings replicate previous reports of cognitive deficits in patients with NMO and show that these deficits manifest in specific cognitive domains. Moreover, this research provides the first evidence that NMO disrupts the ability to recognize negative emotions, including disgust, anger and fear. Interestingly, no covariation was found between emotional and neuropsychological measures. These findings suggest that the impairment of recognize negative valence emotions in NMO patients is independent of other cognitive dysfunctions.

In accordance with previous reports, our results showed that NMO patients performed worse than controls in specific executive tasks involving divided attention, information-processing speed and working memory (Blanc et al., 2008; Blanc et al., 2012; He et al., 2011). This is the first study that has found systematic deficits in verbal inhibitory control, suggesting that executive dysfunction in NMO requires further examination. The impaired ability of NMO patients to perform these cognitive tasks appears to be associated with grey and white matter atrophy in brain regions including the ACC (He et al., 2011), corpus callosum and medial frontal cortex (Blanc et al., 2012; He et al., 2011). However, the specific neurological basis of cognitive impairments in NMO remains largely undetermined.

Recent approaches suggest that rather than restricted to specific and isolated structures, the neuroanatomical basis of the emotional system consists of highly interconnected and distributed brain areas (Kennedy & Adolphs, 2012, Ibanez & Manes, 2012). Facial emotion recognition is a sensitive domain for psychiatric and neurological conditions (Baez et al., 2014; Gonzalez-Gadea et al., 2014; Ibanez et al., 2014; 2013a; 2013b). Similarly, neuroimaging studies support the idea that partially separated neural circuits (see below) underlie the mechanism for recognition of disgust, fear and anger (Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). Several components of the emotional network appear to be affected in NMO (Blanc et al., 2012). For example, (a) the insula and ACC are involved in disgust perception (Phillips et al., 1997; Wicker et al., 2003, Ibanez et al., 2010), (b) the superior temporal gyrus and orbitofrontal cortex are related to anger perception (Adolphs, Tranel, & Damasio, 2003; Grosbras & Paus, 2006; Phillips et al., 1997), and (c) the ACC also plays an important role in fear perception (Adolphs, 2013). Although preliminary, our

behavioral results are consistent with the specific neural network hypothesis of emotional processing (Kennedy & Adolphs, 2012).

Although the visual dysfunction that occurs in NMO patients could have influenced our findings, no differences between the NMO group and the controls on the six neuropsychological subtests involving visual functions were detected.

Our results indicate that the impairment in emotion recognition observed in NMO patients is not dependent on other co-occurring cognitive deficits. In agreement with the recently described social-brain model (Kennedy & Adolphs, 2012, Ibanez & Manes, 2012), we speculate that facial expression recognition is underpinned by a partially independent distributed neural network.

These results contribute to our understanding of the time course of cognitive dysfunction in NMO. Early detection of cognitive deficits could be critical for diagnosing and developing treatment strategies for patients with NMO. These findings also provide evidence to support the distributed neural basis of emotion recognition.

Some important limitations of this study should be noted. First, although we used healthy subjects in a comparison group, we did not test MS patients, a decision that to some extent limits the interpretation of our results. Moreover, the sample size of our groups is small and our result should be considered as preliminary. We cannot exclude the possibility that low power (due to the limited number of participants) may have influenced the results. Reaction times, for example, were longer for the NMO subjects on all emotional recognition measures, and may have reached statistical significance with a larger NMO cohort.

Nonetheless, deficits in emotion recognition were detected in all NMO patients and at this preliminary evaluation, they seems to not be explained by other cognitive deficits.

We have shown that NMO potentially impairs the recognition of negative valance facial expressions independent from its other cognitive effects suggesting a bimodal emotional-cognitive impairment due to NMO pathology. This preliminary evidence opens a new research agenda. Further research should investigate if these impairments are related to damage in critical brain regions underlying emotional neural networks. Future studies should also employ additional social cognition measures to explore the relationship between impaired brain regions and higher order aspects of social cognition in NMO. Neuroimaging studies in patients with NMO and MS should investigate facial expression recognition to provide detailed anatomical evidence to support the results of our research. From a translational perspective, the identification of this unrecognized and unaddressed impairment opens new avenues for intervention programs. This degree of compromised emotional salience on the part of the NMO group is likely to disrupt the quality of life of both the patient and relatives. Intervention programs for NMO should include teaching implicit and explicit rules for interpreting the emotional facial sings in everyday life.

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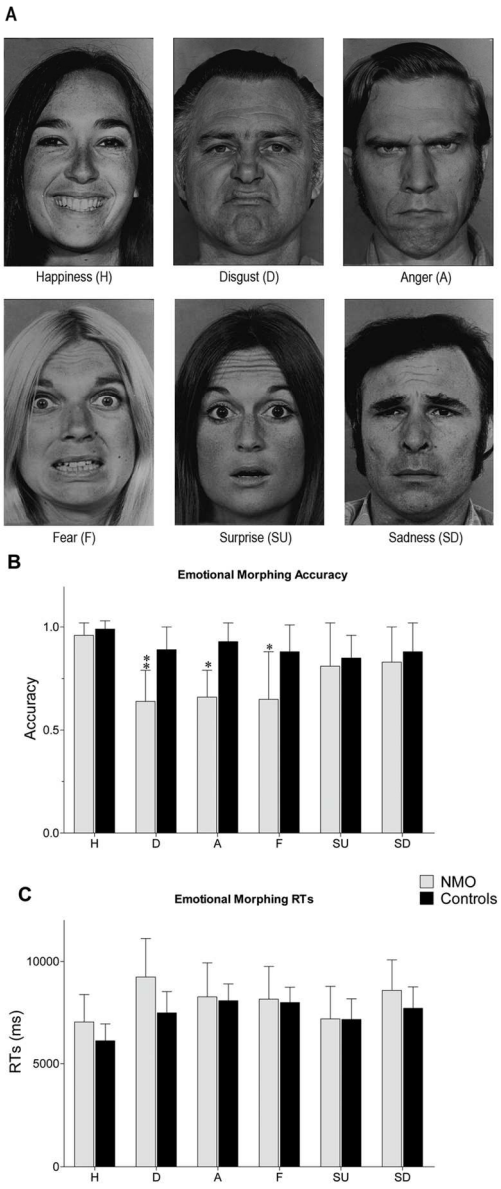
**Table 1.** Main demographic and clinical findings from patients with NMO and control group.

| | NMO Group | Controls |
|---|---|---|
| Sex, F/M | 7/3 | 7/3 |
| Handedness (right/left) | 9/1 | 9/1 |
| Age (Mean±SD) | 40.60±12.88 | 40.70±12.70 |
| Educational level (years) | 13.70±2.31 | 14.90±2.81 |
| Disease duration | 7.40±4.40 | NA |
| First signs | Optic neuritis (n=3), myelitis (n=5), optic neuritis and myelitis (n=2) | NA |
| Positive for NMO-IgG | 100% | NA |
| EDSS score | 2.25±1.01 | NA |

Abbreviations: NMO, neuromyelitis optica; EDSS, Expanded Disability Status Scale; NA, not applicable




(A) Some of the photos of facial expressions used in emotional morphing paradigm; (B) Emotional morphing (accuracy per category). (C) Emotional morphing reaction times.
76x174mm (300 x 300 DPI)

# Supplementary data

## Supp data 1

### Neuropsychological assessment

*The Addenbrooke´s Cognitive Examination Revised* (ACE-R, Torralva et al, 2011) is a brief, sensitive test for the early stages of dementia with the ability to differentiate between different subtypes of dementia, including Alzheimer's disease, Frontotemporal dementia, Progressive supranuclear palsy and other parkinsonian syndromes. In addition, the Mini Mental State Examination (MMSE) was included as a measure of dementia as occurs in Parkinson disease (Chade et al., 2008; Reyes et al., 2009) and other motor disorders (Bak et al., 2005).

*The INECO Frontal Screening* (IFS, Torralva et al., 2009) is a test battery used to assess executive functions including (a) response inhibition and shifting assessed by motor programming, conflicting instructions, Go/No-Go, verbal inhibitory control and proverb interpretation; (b) abstraction and working memory assessed by backwards digit span, verbal working memory and spatial working memory. It takes less than 10 minutes to administer, and it gives a profile of the patient's executive functions.

*The picture version of the Pyramids and Palm Trees Test* (PPT, Howard and Patterson, 1992). The PPT consists of 52 triplets of pictures depicting different objects. Each triplet is composed of a cue object-picture (e.g., spectacles) and two semantically related pictures (eye and ear). Participants are asked to point to the picture that is the most closely related to the cue picture. The relation between the cue picture and the response picture in this task has to be discovered by the subject and differs across trials.

*The picture version of the Kissing and Dancing Test* (KDT). Bak and Hodges(2003) created this test based on the design and size of PPT. The KDT uses 52 triads of images to assess the ability to access semantic representations of verbs and is directly comparable to the 52 triplets of objects of the PPT.

*The Paced Auditory Serial Addition Test* (PASAT- Inter-stimulus time: 3sec, Rao et al., 1990) evaluates working memory, divided attention, information processing speed and calculation ability. From a series of 61 numbers ranging from 1 to 9, a single number was randomly presented to the

participant every 3 seconds. Participants were instructed to add each new digit to the one immediately preceding it. Performance was assessed by the percentage of correct additions.

*The Symbol Digit Modality Test* (SDMT; Smith, 1991) was used to assess information processing speed. Participants were given a reference key that they had to use to help connect basic roman numerals to a series of geometric shapes. Responses were verbal, and the entire test lasted 90 seconds. Scoring and evaluation of the test took five minutes to complete.

**Supp data 2**

The mean scores of all the groups on the Mini Mental State Examination (MMSE), the Addenbrooke's Cognitive Examination - Revised (ACE-R) and the INECO Frontal Screening (IFS) are shown in Table 2. For all scores, data were analyzed by one-way ANOVA comparing performance of patients and controls. Table 3 presents the overall results for both groups.

**Table S1.** Results of Neuropsychological Test in NMO and Controls

| | **NMO Group (n=10)** | **Controls (n=10)** |
|---|---|---|
| **MMSE** | 29.50 (0.71) | 29.70 (0.48) |
| **ACE-R** | **90.10 (4.01)*** | 95.00 (4.85) |
| **INECO FRONTAL SCREENING** | | |
| Motor programming | 3.00 (0.00) | 3.00(0.00) |
| Conflictive Instructions | 3.00 (0.00) | 2.80 (0.42) |
| Go-No Go | 2.80 (0.42) | 2.50 (0.53) |
| Digits backward | 3.50 (1.18) | 4.20(0.92) |
| Verbal working memory | 2.00 (0.00) | 2.00(0.00) |
| Spatial working memory | 3.60 (0.52) | 3.60(0.52) |
| Abstraction capacity | 3.00 (0.00) | 2.90 (0.32) |
| Verbal Inhibitory Control | **3.90 (0.11)**** | 5.70(0.48) |
| **IFS Total Scores** | **24.80 (1.40)*** | 26.70 (2.16) |
| Kissing & Dancing Test | 50.80 (1.32) | 51.60 (.70) |
| Pyramids & Palms Trees | 51.60 (0.52) | 51.50 (0.71) |
| SDMT | **53.10 (14.04)*** | 68.50(18.36) |
| PASAT 3s | **36.70 (9.94)**** | 50.60(4.74) |

Mean (±SD); * P<0.05; ** P<0.001 in NMO vs. control group
Abbreviations: NMO, neuromyelitis optica; MMSE, Minimental State Examination; ACE-R, Addenbrooke's Cognitive Examination; SMDT, symbol digit modalities test; PASAT, Paced Auditory Serial Addition Test

NMO patients did not differ in their scores from the CG in either of the MMSE tasks. Patients with NMO obtained significantly lower scores than the CG in the following tests: ACE-R total score [F(1, 18)=6.0546; p=0.02]; verbal inhibitory control [F(1,18)=22.431; p< 0.001]; IFS total score [F(1, 18)=5.4422; p=0.03]; the symbol digit modalities test of the Wechsler Adult Intelligence Scale-Revised [F(1, 18)=4.4418; p=0.05] and the 3 second PASAT [F(1, 18)=15.917; p<0.001]. These results suggest that NMO patients had impaired short-term memory, decreased information processing speed and partially impaired executive functions.

**Supp data 3**

**Table S2.** Emotional morphing accuracy and reaction times

| | | NMO (N=10) | CTRL (N=10) |
|---|---|---|---|
| Accuracy | Happiness | 0.96(0.06) | 0.99(0.04) |
| | Disgust | 0.64(0.15) | 0.89(0.11)** |
| | Anger | 0.66(0.13) | 0.93(0.09)* |
| | Fear | 0.65(0.23) | 0.88(0.13)* |
| | Surprise | 0.81(0.21) | 0.85(0.11) |
| | Sadness | 0.83(0.17) | 0.88(0.14) |
| RTs | Happiness | 7018.25(1380.47) | 6108.71(824.20) |
| | Disgust | 9250.14(1871.18) | 7462.62(1078.60) |
| | Anger | 8285.79(1649.60) | 8052.10(858.59) |
| | Fear | 8125.27(1637.58) | 7967.41(784.00) |
| | Surprise | 7170.60(1623.84) | 7146.61(996.46) |
| | Sadness | 8601.51(1484.59) | 7686.87(1078.06) |

Mean (±SD); * P<0.05; ** P<0.01

**Supplementary Figure S1**

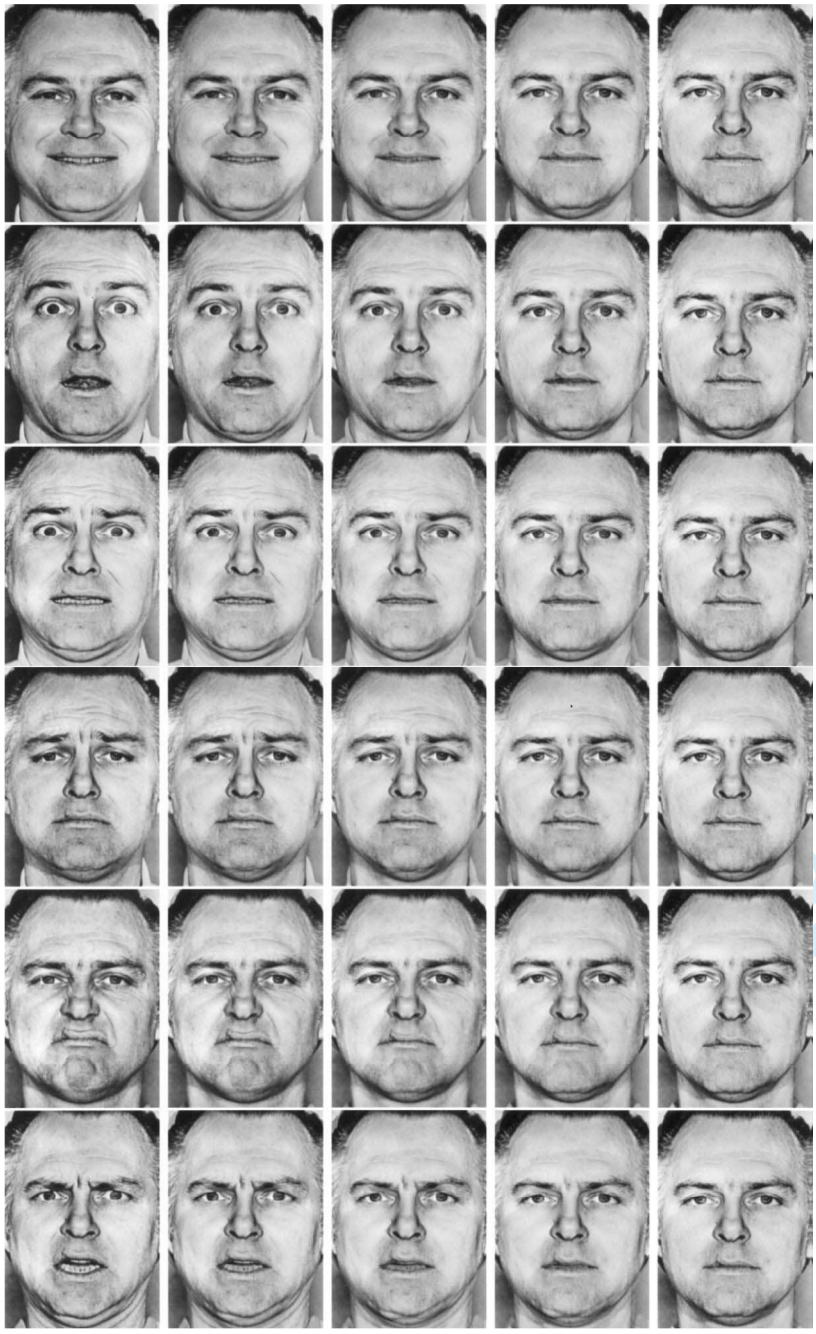


Figure S1. Example of the morphed face paradigm. Going from left to right, the columns show 90%, 70%, 50%, 30% and 10% morphs along each continuum. Fig. 4. Continua including a neutral expression used in Experiment 2. From top to bottom, the continua shown in each row are happiness–neutral (top row), surprise–neutral (second row), fear–neutral (third row), sadness–neutral (fourth row), disgust–neutral (fifth row), anger–neutral (bottom row). Reproduced with permission from Elsevier (Young et al., 1997).

## Supplementary References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