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Anosognosia and neglect respond differently to the same treatments

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Different techniques, such as optokinetic stimulation, adaptation to prismatic shift of the visual field to the right, or transcutaneous electrical nerve stimulation (TENS), have been shown to alleviate neglect, at least temporarily. We assessed the effect of these techniques on anosognosia and whether their therapeutic effect, if any, matches that on neglect. The effect of the three types of treatment on anosognosia and neglect was investigated in five patients presenting with both severe anosognosia and neglect. Patient 1 was treatment responsive to anosognosia but not to neglect, whereas patients 4 and 5 showed the reverse pattern, i.e., they were treatment responsive to neglect but not to anosognosia. This “treatment response bias” proved to be a valid means to investigate different effects of treatments in the same patient.

Keywords: Double dissociation; Neglect; Anosognosia; Treatment.
Unawareness of one’s own motor disorders (anosognosia) is a common, although often fleeting, occurrence following brain damage (Orfei et al., 2007). Anosognosia for one’s own motor deficits is often observed in association with visuo-spatial neglect (Appelros, Karlsson, Seiger, & Nydevik, 2002; Cocchini, Beschin, & Della Sala, 2002; Karnath, Baier, & Nagele, 2005; Kortte & Hillis, 2009; Jehkonen, Laithosalo, & Kettunen, 2006; Prigatano, Matthes, Hill, Wolf, & Heiserman, 2011; Vocat & Vuilleumier, 2010), and their recovery often occurs in parallel (Prigatano & Morrone-Stupinsky, 2010). Moreover, lesion sites overlap in neglect and anosognosia. In particular, damage to the right temporo-parietal junction, the superior and middle temporal gyri and the right insula has been observed both in cases of neglect and anosognosia (Danckert & Ferber, 2006; Karnath & Baier, 2010; Karnath, Renning, Johannsen, & Rorden, 2011; Mort et al., 2003; Vocat & Vuilleumier, 2010; see also for a recent review Orfei et al., 2007).

Due to this association between neglect and anosognosia, it has been suggested that the rehabilitation of anosognosia for hemiplegia also requires improvement of neglect (Bottini et al., 2010). Indeed, cases have been reported of patients whose lack of awareness for motor impairment was ameliorated by caloric vestibular stimulation together with an improvement of their neglect (Cappa, Sterzi, Vallar, & Bisiach, 1987; Rode, Perennin, Honore, & Boisson, 1998; Vallar, Sterzi, Bottini Cappa, & Rusconi, 1990).

However, anosognosia and neglect have also been observed independently from one another (e.g., Berti et al., 2005; Cocchini, Beschin, Cameron, Fotopoulou, & Della Sala, 2009; Vocat, Staub, Stroppini & Vuilleumier, 2010). For instance, Dauriac-Le Masson et al. (2002) reported on two cases of right brain damaged patients showing a clear double dissociation between neglect and anosognosia for motor symptoms, supporting the view that, although frequently associated, anosognosia and neglect may rely on independent mechanisms. Indeed several group studies have pointed out how these two syndromes may be selectively present following brain damage (e.g., Bisiach, Vallar, Perani, Papago, & Berti, 1986; Cutting, 1978) or the Wada procedure (e.g., Adair et al., 1995).

The purpose of the current study was to implement a novel approach based on response to treatment to investigate the clinical outcome of different treatments and the possible dissociations between syndromes often reported as associated.

Different intervention techniques have been proposed to alleviate neglect, at least temporarily (see review by Rossetti & Rode, 2002 and by Jacquin-Courtois, Rode, Pisella, Boisson, & Rossetti, 2008). Treatments which proved effective include optokinetic stimulation (e.g., Salillas, Granà, Juncadella, Rico, & Semenza, 2009), adaptation to prismatic shift of the visual field.
to the side ipsilateral to the lesion (e.g., Rode, Klos, Courtois-Jacquin, Rossetti, & Pisella, 2006; Sarri, Greenwood, Kalra & Driver, 2011; Nijboer, Nys, van der Smagt, van der Stigchel, & Dijkerman, 2011), and transcutaneous electrical nerve stimulation (TENS) (e.g., Schröder, Wist, & Hömberg, 2008). The effects of these treatments on anosognosia have rarely been formally investigated (Rossetti & Rode, 2002; Bottini et al., 2010). This was the purpose of this study. To this end we used a new procedure, which we labelled “treatment response bias”, to investigate whether optokinetic stimulation, prism adaptation and TENS have similar therapeutic effects on anosognosia and neglect.

MATERIALS AND METHODS

Participants

Five patients were recruited for the study from a larger investigation on anosognosia, including both left and right hemisphere damaged patients (Della Sala, Cocchini, Beschin, & Cameron, 2009; Cocchini et al., 2009). They were selected according to the following criteria: (1) CT or MRI-demonstrated first stroke; (2) severe contra-lesional motor impairment; (3) no known previous psychiatric or neurological problems; (4) clear signs of anosognosia for motor impairments; and (5) overt extrapersonal visuo-spatial neglect. Their demographic and clinical features are summarised in Table 1.

Measures of motor impairment

The presence of motor impairment was assessed by means of the Standard Neurological Examination for upper and lower limbs (Bisiach, Perani,

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age</th>
<th>Education (years)</th>
<th>Days post-onset</th>
<th>Lesion side and site</th>
<th>Standardised neurological examination</th>
<th>Motricity Index (100–0)</th>
<th>Barthel Scale – ADL (0–20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 1</td>
<td>F</td>
<td>65</td>
<td>5</td>
<td>60</td>
<td>R FP</td>
<td>3 3 15</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pt 2</td>
<td>F</td>
<td>44</td>
<td>8</td>
<td>60</td>
<td>L FTP</td>
<td>3 3 58</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Pt 3</td>
<td>M</td>
<td>75</td>
<td>8</td>
<td>50</td>
<td>L FP</td>
<td>3 3 1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pt 4</td>
<td>F</td>
<td>64</td>
<td>10</td>
<td>60</td>
<td>R PO</td>
<td>3 2 19.5</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Pt 5</td>
<td>F</td>
<td>62</td>
<td>17</td>
<td>70</td>
<td>L FP</td>
<td>3 2 22</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

R = right lesion; L = left lesion; F = frontal lobe; P = parietal lobe; T = temporal lobe; O = occipital lobe.
Vallar, & Berti, 1986) and by means of the Motricity Index (Wade, 1992). In the Standard Neurological Examination the score for each limb ranged from 0 (normal motor performance) to 3 (complete paralysis). Scores of 1 and 2 were given for mild and moderate motor impairment, respectively. With the Motricity Index, three limb movements of the contra-lesional upper limb were assessed: “pinch grip”, “elbow flexion” and “shoulder abduction”. Following published instructions (Wade, 1992), for each of these movements, a score from 0 (no movement) to 33 (normal power) was given. The score for upper limb movement was then calculated by adding the score for the three movements plus 1, to give a total score between 1 (severe motor impairment) and 100 (no motor impairment). Poor performance due to apraxia, tremor or ataxia was not considered as evidence of paresis in either of the tests used.

All patients were also tested with the Barthel Scale (Wade & Collin, 1988), assessing functional independence in activities of daily living (ADL). The ADL Index addresses 10 items including grooming, incontinence, feeding and dressing, yielding a total score from 0 to 20 (best performance). As shown in Table 1 all patients showed considerable motor impairment and poor independence in everyday activities.

Neuropsychological assessment

**Background neuropsychological measures.** Language abilities were assessed by means of the comprehension and the naming task of the Aachener Aphasia Test (AAT; Huber, Poeck, Weniger, & Willmes, 1994). Verbal intelligence and executive functions were tested by means of the Verbal Judgement Test (Spinnler & Tognoni, 1987) and the Cognitive Estimations Test (Della Sala, MacPherson, Phillips, Sacco, & Spinnler, 2003), respectively. Individual performances are given in Table 2.

<table>
<thead>
<tr>
<th>Verbal Intelligence</th>
<th>Language AAT</th>
<th>Cognitive Estimation Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Judgement</td>
<td>Naming (0–120, cut-off = 108)</td>
<td>Comprehension (0–120, cut-off = 110)</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt 1</td>
<td>42</td>
<td>120</td>
</tr>
<tr>
<td>Pt 2</td>
<td>38</td>
<td>108</td>
</tr>
<tr>
<td>Pt 3</td>
<td>40</td>
<td>111</td>
</tr>
<tr>
<td>Pt 4</td>
<td>56</td>
<td>112</td>
</tr>
<tr>
<td>Pt 5</td>
<td>46</td>
<td>118</td>
</tr>
</tbody>
</table>

Score ranges and cut-off scores are given in brackets. *Below cut-off score.
Assessment of neglect. Presence of neglect was ascertained by means of the Behavioural Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987), testing aspects of visual-spatial neglect by means of six conventional measures. Individual performances are detailed in Table 3. For the purpose of this study and to facilitate the comparison across measures, the percentage of contralesional items incorrectly identified/missed was considered. For example, in the case of line cancellation, the task is to cross out 18 short segments in each half of the array; if a patient with a right hemisphere lesion correctly crossed out 9 segments in the left half side of the array, their score would be 50%. Hence, 100% identifies maximum severity whereas a score of 0 means no neglect. The total “neglect” score has been taken as the average percent across the six measures. Only those tests showing neglect at baseline (i.e., before treatment) were considered for treatment.

Assessment of anosognosia. Anosognosia was assessed by means of a recently validated test, which minimises the need for verbal processing (Cocchini et al., 2009; Della Sala, Cocchini, Beschin, & Cameron, 2009). The test consists of 12 questions considering the patient’s ability to perform tasks that require the use of both hands (8 questions) or both feet (4 questions) (“bilateral tasks”, e.g. walking). Four further questions, which elicit obvious answers (“check questions”, e.g., “Do you have any difficulty in juggling five balls in the air?”) were used to verify the patient’s compliance, comprehension of the questions, or preservation. Control questions were not entered in the final scoring for anosognosia but they established each patient’s response reliability. Finally, two carers (with a personal or a professional relationship with the patient) filled in the questionnaire rating the patient’s motor skills. To diagnose anosognosia, a discrepancy score is calculated by subtracting the mean of the carers’ scores from the patient’s self-evaluation.

### Table 3
Performances of the five patients when first tested on the 6-test neglect battery (BIT) and on the anosognosia assessment (VATAm)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Neglect</th>
<th>Anosognosia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Star Cancellation</td>
<td>Line Cancellation</td>
</tr>
<tr>
<td>Pt 1</td>
<td>100</td>
<td>44</td>
</tr>
<tr>
<td>Pt 2</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>Pt 3</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>Pt 4</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>Pt 5</td>
<td>89</td>
<td>28</td>
</tr>
</tbody>
</table>

0 = absence of the symptom, 100 = max severity.
Further details on the test and scoring procedures are given elsewhere (Della Sala et al., 2009). For the purpose of this study, a positive discrepancy score on the VATA-m was considered as evidence of awareness. To allow further analyses and comparison with other cognitive deficits, these scores were transformed in percentages, where 0% indicates full awareness (discrepancy score = 0) and 100% indicates severe anosognosia (discrepancy score = 36).

Treatments and procedures

The effect of three procedures was assessed: optokinetic stimulation (OPK), prism adaptation (Prism) and transcutaneous electrical nerve stimulation (TENS). The order of stimulation was randomised across patients (see below), and different stimulations were carried out with intervals of at least two days. Neglect tests in which each patient showed neglect at baseline, and the VATA-m were repeated immediately and 48 hours after each stimulation. Procedures for administering the treatments followed those reported in the literature (Rossetti & Rode, 2002). For each treatment the patients were tested before (baseline), immediately after having received the treatment (Time 1) and after 48 hours (Time 2) (see Table 4).

The order of administration of the three procedures was:

Pt1 = Optokinetic, Prism, TENS
Pt2 = TENS, Optokinetic, Prism
Pt3 = Prism, TENS, Optokinetic
Pt4 = TENS, Optokinetic, Prism
Pt5 = Prism, TENS, Optokinetic

Analyses

For any of the three treatments and any of the two conditions (anosognosia and neglect), we wished to measure the effect of that treatment on that condition for an individual patient. An obvious measure of the “treatment effect” for a particular patient would be to take a measure of that patient’s scores immediately before treatment (the “baseline” measure) and subtract the same measure immediately after treatment. Any treatment effect would be shown as a bettering in the target score, i.e., as a positive value of the difference. It is clear that taking the average of two measurements of the baseline value of the deficit will give a more reliable value than just one baseline measurement. If the treatment is known to have only a short-term effect (e.g., Rossetti & Rode, 2002) the baseline value of the deficit can be equally well measured before the treatment, or sufficiently long after the treatment to ensure that any treatment effect has disappeared. In this case, a second measure of deficit taken 48 hours after treatment was considered to be, in effect, another baseline measurement.
### TABLE 4
Performances on neglect and anosognosia of the five patients entering the study

<table>
<thead>
<tr>
<th>Patients</th>
<th>Prismatic stimulation</th>
<th>Optokinetic stimulation</th>
<th>TENS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neglect</td>
<td>Anosognosia</td>
<td>Neglect</td>
</tr>
<tr>
<td>Pt 1</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pt 2</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pt 3</td>
<td>52</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Pt 4</td>
<td>81</td>
<td>63</td>
<td>78</td>
</tr>
<tr>
<td>Pt 5</td>
<td>85</td>
<td>74</td>
<td>89</td>
</tr>
</tbody>
</table>

For each treatment, the patients’ performance at the baseline immediately after having received the treatment and after 48 hours is shown. B = baseline; T = immediately after treatment; P = post-training after 48 hours.
If the measurements taken just before treatment, just after treatment and 48 hours after treatment are denoted by $x_1$, $x_2$ and $x_3$, the algebraic result of subtracting the immediately post-treatment value from the average of the two baseline measurements can be written in the form of a contrast, namely $(x_1 + x_3)/2 - x_2$. We will call the value of this contrast the “treatment response” for a particular treatment on a given condition. This treatment response can be calculated for each individual patient.

In this study, we were interested in the differences between the two conditions under consideration (neglect and anosognosia), and not in the differences between the three treatments. In support of this, the evidence showed that all the treatments have a similar effect on the deficits for individual patients (see Table 4). Indeed when the data from the neglect and anosognosia tests are combined, a repeated measures ANOVA shows that there is no significant difference across the three treatments. Therefore, the power of the analysis can be enhanced by ignoring the differences between the individual treatments and combining the different treatment effects into a single variable by taking their average. For example, from the separate treatment effects of optokinetic, prisms and TENS on neglect, we can derive a contrast representing the “combined treatment response” on anosognosia for a particular patient. If $x$ represents the optokinetic measurements, $y$ the TENS measurements and $z$ that for prisms, the contrast for the “combined treatment response for anosognosia” ($R_a$) would be:

$$R_a = \{(x_1 + x_3)/2 - x_2 + (y_1 + y_3)/2 - y_2 + (z_1 + z_3)/2 - z_2)\}$$

whereby the subscript on the contrast $R_a$ signifies that it relates to anosognosia.

This can now be measured on any one of the five patients. Since this score depends on the patient, we could consider it a characteristic of the individual patient, and as the “combined treatment sensitivity for anosognosia” for that patient. Similarly, we can create a contrast, $R_n$, representing the “combined treatment response for neglect” for a given patient.

For each patient, finally, a single score for $R_{an}$ (i.e., $R_a - R_n$) can be given, representing the relative treatment effects on anosognosia, and neglect, for that patient. We might call this the “treatment response bias” for the patient in the context of comparing anosognosia and neglect. The “bias” here refers to the bias introduced when we shift our attention from one condition (anosognosia) to the other (neglect).

The randomisation was carried out by generating a range of values for $R_{an}$ that one would expect to find on the null hypothesis (i.e., no difference between the conditions). To do this, we needed to form a set of “dummy” values of the contrast $R_{an}$ from the dataset. The contrast involved choosing...
nine values randomly without replacement from the set of data for anosognosia for patients 1, 2, 3, 4 and 5, calculating a value for $R_a$ corresponding to these values, choosing a separate set of nine values from the neglect data for these same patients, calculating in the same way a value for $R_n$, and then calculating the value of $R_{an}$ from this randomisation as $R_a - R_n$. Repeating this randomisation for 1000 trials will produce a dataset from which the standard deviation of $R_{an}$ can be calculated. This randomised result enables us to calculate a $z$-score and hence a significance value for actual values calculated from the data, and will give us a measure of how large, $R_{an}(A) - R_{an}(B)$, for any pair of patients, A and B, needs to be, to declare it significant, and thus a counter-example to the null hypothesis that the patients do not differ. Such a difference will provide something equivalent, by the argument given above, to a double dissociation.

RESULTS

Considering normative data for anosognosia (Della Sala et al., 2009), all patients showed a pathological degree of awareness (severe for patients 1, 3, 4 and 5; moderate for patient 2). Concerning performance on neglect tests, all patients showed neglect on most of the tests. Baseline data were entered on an one-way ANOVA, which showed a significant effect of patients, $F(4, 29) = 5.287; p < .003$. A post-hoc analysis with Bonferroni correction showed that patients 1, 3, 4 and 5 showed a similar degree of impairment, while patient 2 showed a milder form of neglect. Considering descriptive analyses at baseline and immediately after treatment (see Table 4), the five patients showed different patterns of recovery of neglect and anosognosia. Patient 1 did not show any modification on neglect performance with any treatment. However, her awareness increased with all treatments. Patients 4 and 5 showed the opposite pattern of results, that is they showed a clear improvement on neglect with all three treatments, which however had no effect on their awareness. Finally, patients 2 and 3 showed a trend suggesting some improvement of neglect with OPK and TENS, whereas their awareness increased only following Prisms (patients 2 and 3) and TENS (patient 3). A second interesting set of data was that, when a trend of improvement was observed, this vanished within 48 hours. This suggests that the modifications observed did not depend on a general associated spontaneous recovery, but on each specific treatment.

As to the specific question of the treatment bias, the randomisation for the anosognosia/neglect data gave a standard deviation for $R_{an}$ of 20.94. By a standard formula, the standard deviation of the difference of two values of $R_{an}$ for two separate patients should be $20.94 \times \sqrt{2}$, or 29.6. Dividing the difference, $R_{an}(A) - R_{an}(B)$, for any pair of patients, A and B, by 29.6 will then
give a \( z \)-score for this difference, which can then be converted into a two-sided \( p \)-value from a conversion table. To allow for inflation of type I error, we adopted the conservative Bonferroni correction. In this case, as there are five patients and therefore 10 possible pairings, we multiplied the observed \( p \)-values to obtain values which can be compared with the usual alpha level of .05 to determine significance.

A statistical test based on the randomisation described above shows that there are pairs of patients in our sample which differ significantly in their treatment response biases, because for this pair, the data yield significantly non-zero values of \( R_{an}(A) - R_{an}(B) \), and this shows that the conditions themselves are non-identical. When this was done, two and only two pairs attained significance, namely the values for patients 1 and 4, and for patients 1 and 5. The corrected \( p \)-values for these two pairs were .021 and .018, respectively, both significant. In both cases, patient 1 was treatment responsive to anosognosia but not to neglect, and the other two patients showed the reverse pattern, i.e., they were treatment positive to neglect but not to anosognosia.

**DISCUSSION**

We showed that, at least in one case (patient 1), all the three treatments tested had a transient effect only on anosognosia, while on two further cases only prismatic stimulation (patients 2 and 3) or TENS (patient 3) proved to be beneficial, albeit temporarily. This confirms earlier observations (Rossetti & Rode, 2002; Bottini et al., 2010) that some of the treatments proposed to alleviate neglect, might sometimes also be used to improve anosognosia.

Remarkably, the patient who showed a fleeting improvement of her anosognosia is not one of those showing improvement on neglect. This cannot be considered a full blown classic double dissociation, which would require the demonstration that one given treatment has a consistent effect on neglect but not on anosognosia while another treatment shows the opposite outcome. However, the procedure that we used is somewhat reminiscent of a crossover interaction, whereby a patient’s performance to a treatment shows a slope in one direction, and another patient’s data show a pattern in the opposite direction. A dissociation of treatment effect can, we suggest, exist in this case in which \( R_{an}(A) \) and \( R_{an}(B) \) differ, without necessarily having opposite signs. In a \( 2 \times 2 \) ANOVA, it is well known that the test for an interaction effect is equivalent to a test of significance on a single interaction contrast, obtained by subtracting one simple main effect from the other. The analogous situation is obtained here by subtracting the two response profile measures from each other to obtain a single contrast, \( R_{an}(A) - R_{an}(B) \), which should be zero under the null hypothesis. The null hypothesis
states that the two conditions (anosognosia and neglect), which might or might not be due to the same cause, are subsumed by an identical mechanism.

We can argue that variations between patients in both $R_a$ and $R_n$ should be due to two components: the severity of the underlying condition, and a possible effect due to treatment sensitivity, which may differ between patients. However, when we subtract the two contrasts ($R_a$ and $R_n$), individual differences between patients due to these two factors should cancel one another out, and the derived contrast $R_{an}$ should be equal (to within the limits of statistical error) for all patients. This of course will only happen if the null hypothesis is true. Therefore, since we have shown that $R_{an}$ does in fact differ significantly between pairs of patients, we can argue that neglect and anosognosia have different responses to treatment and therefore are not always manifestations of the same and only the same condition.

In conclusion, the treatment response bias represents a suitable, additional method to investigate outcomes of different rehabilitation treatments in relatively small groups of patients who show combinations of different symptoms.

REFERENCES


