

The effects of the dopamine agonist rotigotine on hemispatial neglect following stroke

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Hemispatial neglect following right-hemisphere stroke is a common and disabling disorder, for which there is currently no effective pharmacological treatment. Dopamine agonists have been shown to play a role in selective attention and working memory, two core cognitive components of neglect. Here, we investigated whether the dopamine agonist rotigotine would have a beneficial effect on hemispatial neglect in stroke patients. A double-blind, randomized, placebo-controlled ABA design was used, in which each patient was assessed for 20 testing sessions, in three phases: pretreatment (Phase A1), on transdermal rotigotine for 7–11 days (Phase B) and post-treatment (Phase A2), with the exact duration of each phase randomized within limits. Outcome measures included performance on cancellation (visual search), line bisection, visual working memory, selective attention and sustained attention tasks, as well as measures of motor control. Sixteen right-hemisphere stroke patients were recruited, all of whom completed the trial. Performance on the Mesulam shape cancellation task improved significantly while on rotigotine, with the number of targets found on the left side increasing by 12.8% ($P = 0.012$) on treatment and spatial bias reducing by 8.1% ($P = 0.016$). This improvement in visual search was associated with an enhancement in selective attention but not on our measures of working memory or sustained attention. The positive effect of rotigotine on visual search was not associated with the degree of preservation of prefrontal cortex and occurred even in patients with significant prefrontal involvement. Rotigotine was not associated with any significant improvement in motor performance. This proof-of-concept study suggests a beneficial role of dopaminergic modulation on visual search and selective attention in patients with hemispatial neglect following stroke.

Keywords: neglect; inattention; dopamine agonist; working memory; attention

Introduction

Hemispacial neglect is a common disorder, most pronounced and long-lasting after right-hemisphere stroke, with up to two-thirds of such patients affected in the acute phase (Stone *et al.*, 1991; Bowen *et al.*, 1999). These individuals demonstrate a striking failure to acknowledge or respond to people or objects to their left and are often oblivious of their existence. Enduring neglect has repeatedly been recognized as a poor prognostic indicator for functional independence following stroke (Denes *et al.*, 1982; Fullerton *et al.*, 1988; Kalra *et al.*, 1997; Jehkonen *et al.*, 2000; Cherney *et al.*, 2001). However, despite its clinical impact, the syndrome is underdiagnosed (Edwards *et al.*, 2006; Menon-Nair *et al.*, 2006), and treatment options remain extremely limited. Although several studies have shown promising effects of non-drug interventions such as prismatic deviation or alerting (Rossetti *et al.*, 1998; Wilson *et al.*, 2000; Barrett *et al.*, 2006; Luauté *et al.*, 2006), there is no established drug therapy that has been adopted for clinical use (Lincoln and Bowen, 2006; Bowen *et al.*, 2007).

Rather than being a unitary disorder, neglect is a syndrome consisting of several component deficits (Heilman and Valenstein, 1979; Mesulam, 1999; Husain and Rorden, 2003; Hillis, 2006; Bartolomeo, 2007), with different patients suffering different combinations of cognitive impairment (Buxbaum *et al.*, 2004). For example, difficulties in disengaging or directing spatial attention, initiating or executing movements, sustaining attention over time and representing space to the left have all been reported in individuals with the syndrome (Posner *et al.*, 1984; Gainotti *et al.*, 1991; Robertson *et al.*, 1997a, 1998; Bartolomeo *et al.*, 1998; Mattingley *et al.*, 1998; Bisiach and Luzzatti, 1978; Bartolomeo and Chokron, 2002; Coulthard *et al.*, 2006). A potentially important component demonstrated in recent studies is a deficit in remembering spatial locations over brief periods of time or spatial working memory (Wojculik *et al.*, 2001; Pisella *et al.*, 2004; Malhotra *et al.*, 2005; Mannan *et al.*, 2005; Ferber and Danckert, 2006; Parton *et al.*, 2006), which can interact with deficits in sustained attention to exacerbate neglect (Malhotra *et al.*, 2009).

Dopamine within prefrontal cortex has now been established to play a crucial role in both attention and working memory. Landmark studies in monkeys have shown that visuospatial working memory in monkeys is modulated by dopamine (Funahashi and Kubota, 1994; Goldman-Rakic, 1996; Goldman-Rakic *et al.*, 2000), specifically via prefrontal dopamine D₁ receptors (Williams and Goldman-Rakic, 1995). Indeed, a selective D₁ agonist can enhance working memory in aged monkeys (Castner and Goldman-Rakic, 2004) or reverse experimentally induced spatial working memory deficits (Castner *et al.*, 2000). In healthy humans too, D₁—but not D₂—dopamine receptor agonists can facilitate spatial working memory (Müller *et al.*, 1998).

In addition to its pivotal role in working memory, new findings suggest that frontal D₁ receptor activity can have long-range, modulatory effects on visual areas subserving attention. Thus, local infusion of a D₁ antagonist into monkey frontal cortex not only modulated the firing of neurons in visual cortex but also

altered the animal's ability to select visual targets (Noudoost and Moore, 2011). Furthermore, dopaminergic neuronal networks have a well-recognized role in alerting or allocating attention to unexpected sensory cues based on the potential importance or behavioural relevance of the stimulus (Bromberg-Martin *et al.*, 2010). These findings raise the possibility of modulating D₁ receptor activity to alter attention and/or working memory and thereby ameliorate neglect in stroke patients.

There have previously been few attempts to test modulation of dopaminergic activity as a therapeutic option in hemispacial neglect, but the largest trial tested only four patients. Despite some initial promising results from an open-label study in two patients using bromocriptine, a predominantly D₂ dopamine receptor agonist (Fleet *et al.*, 1987), a further small open-label trial and a case report revealed worsening of neglect with the drug (Grujic *et al.*, 1998; Barrett *et al.*, 1999). Apomorphine, which has both D₁ and D₂ receptor activity, induced a transient improvement in three of four neglect patients tested (Geminiani *et al.*, 1998). In keeping with this finding, an open-label study showed some improvement in standard neglect tests following treatment with levodopa in three of four cases studied (Mukand *et al.*, 2001). Finally, a small-scale trial of amantadine in four neglect patients did not demonstrate any beneficial effect of the drug (Buxbaum *et al.*, 2007).

We conducted a double-blind, randomized, placebo-controlled trial of the dopamine agonist rotigotine in 16 patients with hemispacial neglect and unilateral weakness following right-hemisphere stroke. In contrast to the substances tested in previous studies, we used rotigotine, which has high affinity for the D₁ receptor compared with many other licensed oral dopamine agonists (Jenner, 2005; Naidu and Chaudhuri, 2007). Our primary objective was to evaluate whether the drug improves neglect and its cognitive components, including selective and sustained attention, as well as spatial working memory. A further aim was to assess the effects of rotigotine on motor performance, because some previous studies have suggested that levodopa may have a positive effect on motor deficits following stroke (Scheidtmann *et al.*, 2001; Scheidtmann, 2004; Floel *et al.*, 2005). Since prefrontal cortex is an important potential candidate area for the cognitive effects of dopamine agonists, we sought to determine whether any beneficial effects of rotigotine depend on the extent of preservation of the right prefrontal cortex.

Patients were assessed with a battery of standardized neglect tests, as well as with tests of working memory, selective and sustained attention and motor function. We used a replicated ABA double-blind, placebo-controlled N-of-1 randomized design, which allowed us to evaluate the effectiveness of an intervention in small sample sizes. Each patient's performance was measured in three phases, each consisting of several assessment sessions: before treatment (Phase A1), while receiving transdermal rotigotine (Phase B) and after discontinuation of the drug (Phase A2). Crucially, the exact duration of each phase was randomized across patients. Performance on rotigotine was compared with the pre-treatment baseline and post-treatment follow-up phases.

The principles of randomized N-of-1 designs (Edgington and Ongheena, 2007), such as the one used here, were originally described by Fisher (1935) for intervention studies, but were

difficult to conduct on a large scale because they require substantial computing power. As a result, few investigators used them. However, modern-day computers make the mathematical demands far less problematic and replicated randomized N-of-1 designs provide a powerful way to assess effects in highly focused studies using a large number of assessments on small patient samples. Randomization or permutation tests are used for analysis of these designs. Importantly, such tests are distribution-free. They are based simply on rearrangements of raw scores. They compare a computed statistic (e.g. the difference in means or medians between two conditions) with the value of that statistic for all other possible arrangements of the data obtained in that patient. The *P*-value is simply the proportion of arrangements leading to a value of the statistic as large as, or larger than, the value obtained from the actual data. The key question is how likely is it by chance that a difference in means was as large as the observed difference between two conditions, e.g. treatment versus no treatment.

In the design used here (Fig. 1), we can compare the difference in mean scores between two phases of the trial, e.g. OFF treatment (Phase A1 and Phase A2) compared with ON drug

(Phase B). Suppose the difference in mean scores ON versus OFF treatment for the patient who underwent the protocol shown in Fig. 1A is *Z*. Randomization tests consider all other possible rearrangements of the data for this patient, within the constraints of the trial design (Fig. 1B). For each of these different permutations of when the drug might start and duration of treatment, the difference in means for each possible A1, A2 and B period is computed using the data set from the patient. Then the probability that other possible rearrangements of the data result in a value as large as, or larger than, *Z* is calculated. This simple permutation principle allows us to ask whether there was a significant change in performance ON drug by comparing the actual difference in means ON and OFF treatment, with all the other potential differences in means. If the drug has a significant effect during the period it is given, we would expect that the mean of performance ON the drug compared with periods OFF would be larger than all the other possible arrangements of the data set from this patient.

Note that this particular patient only had the drug for the period shown in Fig. 1A, but the data from the patient are simply

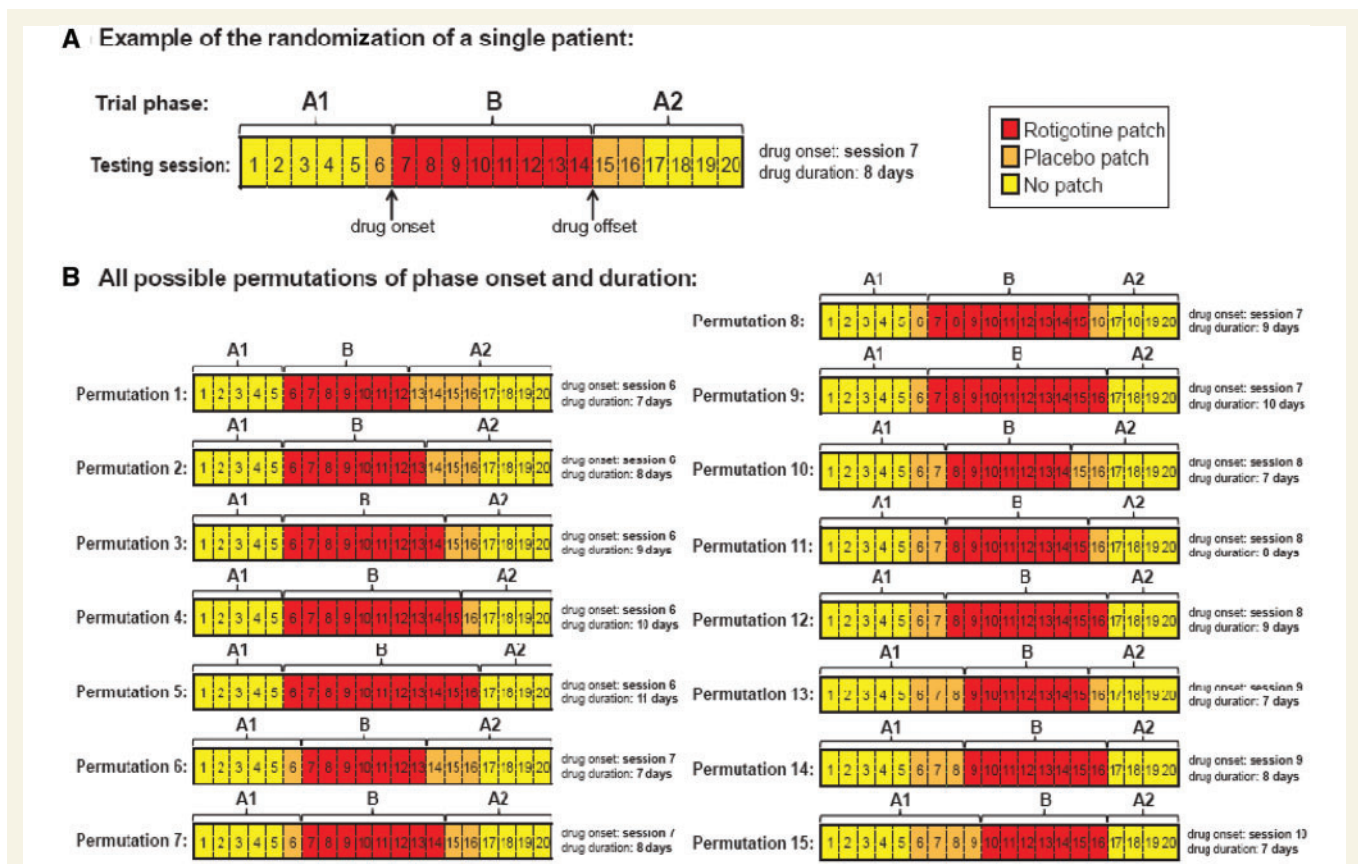


Figure 1 Randomization of treatment allocation and permutation tests. (A) Randomization profile for a single patient. In this case, the treatment phase with rotigotine (Phase B, denoted in red) started on Day 7, and its duration was randomized to 8 days. Therefore, the patient participated in six baseline assessments (Phase A1, Sessions 1–6) and six follow-up sessions after discontinuation of rotigotine (Phase A2, Sessions 15–20). Placebo patch sessions are denoted in orange while sessions without any patches are shown in yellow. The actual difference in performance between treatment (Phase B) and the OFF treatment phases (A1 and A2) was ranked against the differences between phases produced by all other possible combinations of treatment allocation, given the limits in phase onset and duration. (B) All the possible permutations of pretreatment (Phase A1), treatment (Phase B) and post-treatment phase (Phase A2).

reshuffled to produce potential means for ON and OFF treatment if the drug period had been as shown for all the other permutations. If there is no significant effect of drug, we would expect the actual difference in mean performance ON and OFF drug to be very similar to the means from all other possible permutations from this data set. In effect, therefore, each patient acts as their own control. We calculate what the means would have been for Phases A1, B and A2, as if the patient had started the drug a day earlier or a day later or even 2 days later; or if the time on the drug had been longer or shorter than it actually was within the constraints of all the permutations possible (Fig. 1B). Then we compare the differences in means for all these permutations with the actual, observed difference in means ON and OFF treatment. The *P*-value gives us the likelihood of obtaining a value as large as *Z* by chance, computed from the data set of the patient, not by comparing mean scores across patients randomized to receiving treatment or no treatment. Individual *P*-values are then combined to obtain a *P*-value for the entire patient group and separately for two subgroups with different degrees of prefrontal lesion involvement by stroke.

Materials and methods

Patients

Individuals older than 18 years with left hemispatial neglect and a motor deficit due to their first-ever clinically defined right-hemisphere stroke were prospectively recruited from referrals to the trial team at The National Hospital for Neurology and Neurosurgery, London. Left hemispatial neglect was defined as a significant deficit in finding leftward targets on standard cancellation or visual search tasks, using established criteria (Wilson *et al.*, 1987; Gauthier *et al.*, 1989; Mesulam, 2000). A deficit on the line bisection test alone was not sufficient for inclusion. Motor deficit was defined as weakness of at least wrist and finger extension and finger abduction to $\leq 4+$ on the Medical Research Council scale. Patients were eligible only if stroke onset was at least 9 days before the first assessment session.

Exclusion criteria were as follows: a pre-existing neurological condition (e.g. dementia, Parkinson's disease, multiple sclerosis) that would confound cognitive or motor assessments; acute concomitant illness (e.g. infection, unstable angina, myocardial infarction or heart, respiratory, renal or liver failure); systolic blood pressure < 120 mmHg and/or diastolic < 70 mmHg (as dopamine agonists may lead to postural hypotension, especially during dose escalation); exposure to any other investigational drug within 30 days of enrolment in the study; presence of clinically significant drug or alcohol abuse within the previous 6 months; pregnancy; and breast-feeding.

All patients provided written informed consent before participating in the trial. The study protocol and all relevant documents and procedures were approved by the National Research Ethics Service and the Medicines and Healthcare products Regulatory Agency.

Lesion analysis

According to our hypothesis, the major target of rotigotine for cognitive effects is likely to be dopamine D_1 receptors in prefrontal cortex. Therefore, to assess whether response to rotigotine depends on the degree of preservation of the prefrontal cortex, we stratified the

patients into two subgroups according to the extent of the prefrontal cortical involvement, as quantified by high-resolution MRI. To this end, we used the lesion mapping technique described in Mort *et al.* (2003). Briefly, each patient's stroke lesion was manually delineated at every single axial slice of their native T_1 MRI as a 3D volume of interest using MRICron software (Rorden and Brett, 2000), <http://www.cabiatl.com/mricron/>. The volume of interest of each patient's lesion was then registered to a standard Montreal Neurological Institute (MNI) T_1 template in SPM8b (<http://www.fil.ion.ucl.ac.uk/spm/>), applying cost function masking of the lesioned area to obtain optimal normalization (Brett *et al.*, 2001). Then, the percentage of prefrontal involvement was quantified for each patient, by comparing their normalized brain lesion to a prefrontal template, defined using the PickAtlas SPM toolbox (<http://fmri.wfubmc.edu/software/PickAtlas>).

Study design

We used a double-blind, placebo-controlled 'ABA' randomized design consisting of three consecutive phases: (i) baseline pretreatment phase (Phase A1); (ii) treatment with rotigotine transdermal patches (Phase B) and (iii) post-treatment phase (Phase A2).

The duration of each phase was randomized within limits, such that, in each patient, A1 + B + A2 consisted of a total of 20 assessment sessions. However, the precise durations of A1, B and A2 varied across individuals, with both patients and investigators blind to the precise duration of each of these phases in any given patient. Note that in this design, all patients receive placebo and drug at different stages of the trial, with the exact time at which drug is started and the duration of treatment randomized across individuals.

Phase A1 started on Session 1 and its duration was randomized (across individuals) to between 5 and 9 days. Observations during this phase established the baseline performance. Phase B, when rotigotine was administered, could commence on Day 6 to Day 10, and its duration was a minimum of seven and a maximum of 11 sessions. Finally, Phase A2, when patients were assessed after the discontinuation of rotigotine, was randomized to begin between Sessions 13 and 17 and it lasted for the remaining four to eight sessions.

For the purpose of placebo control, all patients received a placebo patch in the period between Sessions 6 and 16, on the days they were not receiving rotigotine. Placebo and rotigotine patches were visually identical. All investigators, clinical staff, patients and carers were masked to treatment assignment.

Each patient was randomly assigned a pattern of onset and duration of the treatment and baseline phases, within the duration limits described above. As an example, the randomization profile of one of the participants is presented in Fig. 1A. In this example, the patient had six baseline assessments, followed by 8 days on rotigotine (Sessions 7–14) and six follow-up assessments after discontinuation of the drug. In Fig. 1A, the yellow shading shows the minimum number of sessions in Phases A1 and A2, while red shading denotes the treatment phase (Phase B). Orange depicts any additional sessions in Phases A1 and A2 when the patient received placebo patches. All possible permutations of pretreatment, treatment and post-treatment phases within the constraints of the design are shown in Fig. 1B. In total, there were 15 possible permutations.

Clinical and behavioural testing

Each patient participated in 20 consecutive assessment sessions. The first 17 sessions were performed daily. The final three follow-up assessments were conducted at weekly intervals. Each session consisted

of tests of spatial neglect, spatial working memory, selective and sustained attention and motor performance.

Spatial neglect was evaluated with the line bisection test from the Behavioural Inattention Test Battery (Wilson *et al.*, 1987) and with three visual search tasks: Mesulam shape cancellation (Mesulam, 2000) and bells cancellation task (Gauthier *et al.*, 1989), performed on A3 sheets, and a visual search task performed on a touch screen (18 inch diagonal), in which no visible markings were left at the location of the cancelled targets (Parton *et al.*, 2006). There was a 2-min time limit for all visual search tasks.

Spatial working memory was measured with a vertical analogue of the Corsi spatial span test (Malhotra *et al.*, 2005), and also using the rate of revisiting of previously cancelled targets obtained from the touch screen visual search task (Mannan *et al.*, 2005; Parton *et al.*, 2006). Selective attention and sustained attention were assessed using a visual salience and vigilance task, which has been previously used in patients with prefrontal lesions (Barcelo *et al.*, 2000). As shown in Fig. 7A, in this task, participants were asked to detect targets (inverted triangles) among sequences of distractors (upright triangles) randomly presented to the ipsilesional and contralesional visual fields and to respond to targets with a speeded button press. Targets could be of the same colour as the distractors (low visual salience) or of a different colour (high visual salience targets). As a measure of selective attention, we used the ratio of the reaction time to high visual salience targets over the reaction time to low visual salience targets. Furthermore, using this task, we quantified sustained attention over time, by measuring the difference in reaction time and per cent correct responses between the first and the second half of each experimental session.

Motor performance was evaluated in all patients using the Motricity Index (Wade, 1992; Bohannon, 1999) and with grip and pinch dynamometry (Sunderland *et al.*, 1989). Where the patient's level of weakness permitted, motor performance was also assessed using the nine-hole peg test (Mathiowetz *et al.*, 1985b), box and blocks test (Mathiowetz *et al.*, 1985a) and timed 10 m walk (Wade, 1992).

Drug and placebo administration

During the treatment phase, a rotigotine 9.0 mg skin patch (equivalent to 4 mg/24 h transdermal absorption) was applied daily by the investigator. Patients were instructed to wear it 24 h a day. Since rotigotine takes up to 24 h to reach steady-state levels, application of the drug patch started immediately after behavioural testing the day before the drug would be effective. Thus, a patch (drug/placebo) was applied on the last session of Phase A1 and immediately after behavioural testing in Sessions 5–15. Therefore, either placebo or rotigotine was in place during behavioural testing in Sessions 6–16. In the example shown in Fig. 1A, the patient had a placebo patch applied immediately after behavioural testing on Day 5 and an active rotigotine patch was applied after testing on Day 6; the treatment Phase B commenced on Day 7.

To prevent nausea, a common adverse effect of dopamine agonists, patients received domperidone 10 mg orally three times daily from Sessions 1–16. As domperidone does not penetrate the blood–brain barrier, it should not interfere with the central response to rotigotine (Quinn *et al.*, 1981). Blood pressure and pulse were recorded and patients were asked to report any adverse events at each assessment session.

Statistical analysis

We used a replicated randomized N-of-1 design (Edgington and Onghena, 2007), which makes it possible to investigate the effects of an intervention on small groups of patients, provided sufficient assessments are made. Hence, the intensive testing procedure consisted of 17 consecutive daily assessments, followed by three weekly ones. This design methodology, the principle of which was developed by Fisher (1935), is sometimes also referred to as permutation testing. Critically, it makes no assumptions about the underlying distribution of the data (Todman and Dugard, 2001) and has been shown to be particularly robust for studies with small sample sizes (Guyatt *et al.*, 1990; Ferron and Onghena, 1996).

The aim of our analysis was to identify whether performance during the treatment phase (B) was significantly improved when compared with the pretreatment baseline (Phase A1) and with the post-treatment follow-up (Phase A2). For each patient and each outcome measure, we first computed three statistics expressing the difference between phases: (i) difference of the median observation of Phase B from the median of Phase A1 ($B - A1$); (ii) difference between the medians of Phases B and A2 ($B - A2$) and (iii) difference between the median of Phase B and the median of Phases A1 and A2 averaged ($B - Am$). Therefore, $B - Am$ is the difference between the median of the treatment phase (B) and the average of the medians of both OFF treatment phases.

Then each of these measures was ranked against the values of the same measure computed for all possible rearrangements of the data. An example of this approach is presented in Fig. 1B. The higher the ranking of the actual difference ON and OFF rotigotine among all possible permutations, the higher the probability that the observed difference was due to the drug. Based on this ranking, for each outcome measure, we obtained a *P*-value for each individual patient. This *P*-value is derived from the proportion of arrangements leading to a difference between phases which is as large as, or larger than, the difference ON and OFF treatment obtained from the actual data.

A group *P*-value was obtained for each outcome measure, by combining the individual patients' *P*-values, using Edgington's additive method (Edgington, 1972). The same method was used to obtain *P*-values for each of the prefrontal subgroups. Analyses were performed using the *R* statistical software (<http://www.r-project.org/>). Trial design and analyses were implemented by an expert statistician (E.K.).

Results

Sixteen patients fulfilling the inclusion criteria were prospectively enrolled in the trial. Patient demographics are presented in Table 1, and lesion maps are shown in Fig. 2. Compliance with the treatment protocol was 100%; none of the patients missed any dose of rotigotine or placebo. All patients attended 20 assessment sessions as per protocol, apart from Patient 7 who missed one session (Session 11, ON rotigotine), for reasons unrelated to the trial. There were no serious adverse events during treatment with rotigotine. Mild adverse effects included fatigue, mild skin irritation at the site of the patch, and gastrointestinal disturbance, including nausea, vomiting and diarrhoea, which are all known potential side effects of rotigotine (Table 2). Importantly, neither treatment nor assessments were interrupted due to adverse events.

Table 1 Patient demographics and Mesulam search task results

Patient ID	Age	Gender	Handedness	Stroke type	Days post stroke	Prefrontal involvement (%)	Mesulam left targets OFF drug	Mesulam left targets ON drug	Mesulam right targets OFF drug	Mesulam right targets ON drug
P1	42	Male	Right	Ischaemic	728	39.4	13.25	22	26.5	26
P2	62	Male	Right	Ischaemic	70	14.6	24.75	22.5	25.5	27.5
P3	46	Male	Right	Ischaemic	1381	32.5	1.5	5	24.5	27
P4	63	Female	Right	Ischaemic	42	11.8	0.25	0	20.75	23
P5	58	Male	Right	Ischaemic	327	35	0	0	13.5	13
P6	66	Male	Right	Ischaemic	202	54.7	1	0	18	19
P7	62	Male	Right	Haemorrhagic	232	0.2	1.75	2.5	16.75	16
P8	74	Male	Right	Ischaemic	341	35.3	9.75	10.5	22	19.5
P9	53	Male	Left	Ischaemic	385	5.6	22	28	27	29
P10	24	Male	Right	Haemorrhagic	221	7.2	0	0	16.25	8
P11	60	Male	Right	Haemorrhagic	1990	2.4	10.75	20.5	23.25	25.5
P12	62	Male	Right	Ischaemic	941	33.5	2	0.5	26	28
P13	72	Female	Right	Haemorrhagic	1712	32.6	2	8	25.5	22
P14	80	Male	Right	Ischaemic	30	0	22.75	23	24.25	26
P15	51	Male	Right	Haemorrhagic	104	52.9	6.5	7	23.25	23
P16	49	Male	Right	Ischaemic	85	9.1	11.75	13	20.25	18

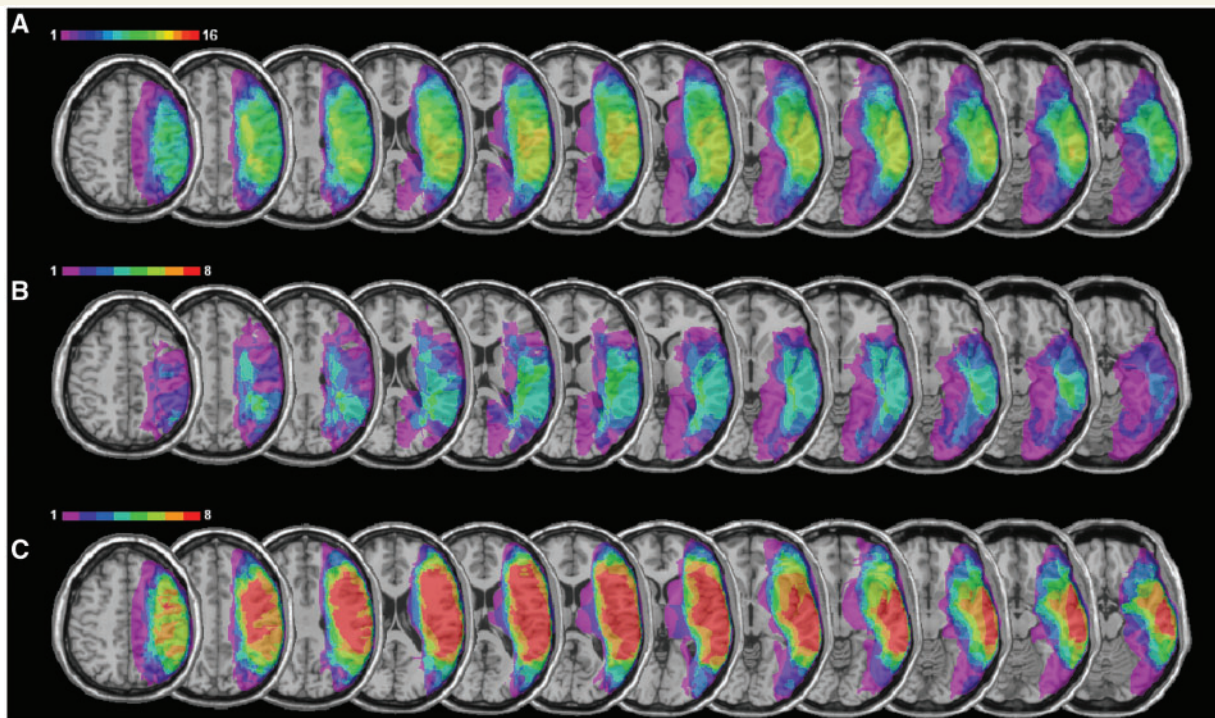


Figure 2 Lesion overlap maps. Axial MRI slices of stroke lesions in (A) the entire group of all 16 patients, (B) the minimal prefrontal involvement subgroup (eight patients) and (C) the extensive prefrontal involvement subgroup (eight patients). Colour values represent the number of patients in whom a given voxel was lesioned; note the scale is different for the entire group (A) compared with the subgroups (B and C).

Treatment with rotigotine was associated with significant improvement in visual search, as quantified by the Mesulam shape cancellation task. As shown in Fig. 3, for the entire group of 16 neglect patients, the number of targets found on the left side was

significantly higher while ON rotigotine than in the pre- and post-treatment phases averaged ($P = 0.012$) or in the post-treatment phase alone ($P = 0.039$). Overall, the difference ON and OFF treatment in the number of targets found on the left side relative

to baseline was 12.8% higher in the actual treatment allocation than the mean difference between phases produced by all possible combinations of treatment onset and duration (Fig. 1). Although the number of targets found on the right side was somewhat decreased ON treatment (Fig. 3), the relative difference ON and OFF treatment was only 0.7% smaller in the actual treatment allocation when compared with all possible permutations, and this was not statistically significant ($P = 0.466$).

Spatial bias in visual search (ratio of difference in the number of targets found on either side to total number of targets found on the Mesulam test) also improved significantly on rotigotine when

compared with the post-treatment phase ($P = 0.018$) or with both OFF treatment phases ($P = 0.016$, Fig. 3). There was 8.1% less rightward bias relative to baseline in the actual treatment allocation, in comparison to all possible permutations (Fig. 4B).

Next, we evaluated the effect of rotigotine on performance on the Mesulam test in two patient subgroups, defined according to the extent of involvement of the prefrontal cortex in the stroke lesion: a minimal prefrontal involvement subgroup (0–15% of the prefrontal cortex affected, Fig. 2B) and an extensive prefrontal subgroup (33–55% of the prefrontal cortex affected, Fig. 2C). A significant benefit of treatment with rotigotine was noted in both subgroups (Fig. 5), but for different study parameters.

The number of targets found on the left was significantly higher ON rotigotine than OFF treatment in the minimal prefrontal subgroup ($P = 0.036$), while this effect did not reach significance in the extensive prefrontal subgroup ($P = 0.084$). Conversely, spatial bias improved significantly ON rotigotine in the extensive prefrontal group ($P = 0.018$), but not in the minimal prefrontal group ($P = 0.177$). Therefore, rotigotine was associated with significant improvement in the Mesulam shape cancellation task in the entire patient group and in both prefrontal subgroups, but the significant measures varied between the two subgroups.

The effect of rotigotine on performance on the Mesulam cancellation task was also assessed on a subject-by-subject basis (Fig. 6 and Table 1). Response to the drug was characterized by considerable variability, with some subjects showing remarkable improvement ON the drug when compared with average performance in the phases OFF rotigotine and others showing smaller positive effects or even a small decline in the number of targets found on the left side while ON the drug (Table 1). The results of

Table 2 Adverse events

	Rotigotine		Placebo	
	Number of patients	Patient (occurrences)	Number of patients	Patient (occurrences)
Fatigue	4 (25%)	P8 (1), P9 (3), P10 (2), P14 (1)	1 (6%)	P9 (1)
Topical skin reaction	1 (6%)	P6 (3)	0	
Nausea	5 (31%)	P1 (1), P3 (1), P4 (2), P8 (3), P9 (2)	0	
Vomiting	1 (6%)	P3 (1)	0	
Diarrhoea	2 (13%)	P4 (2), P8 (1)	0	

Number of patients who had at least one adverse event, patient codes (corresponding to those in Table 1) and number of occurrences per patient on rotigotine and on placebo. P = Patient.

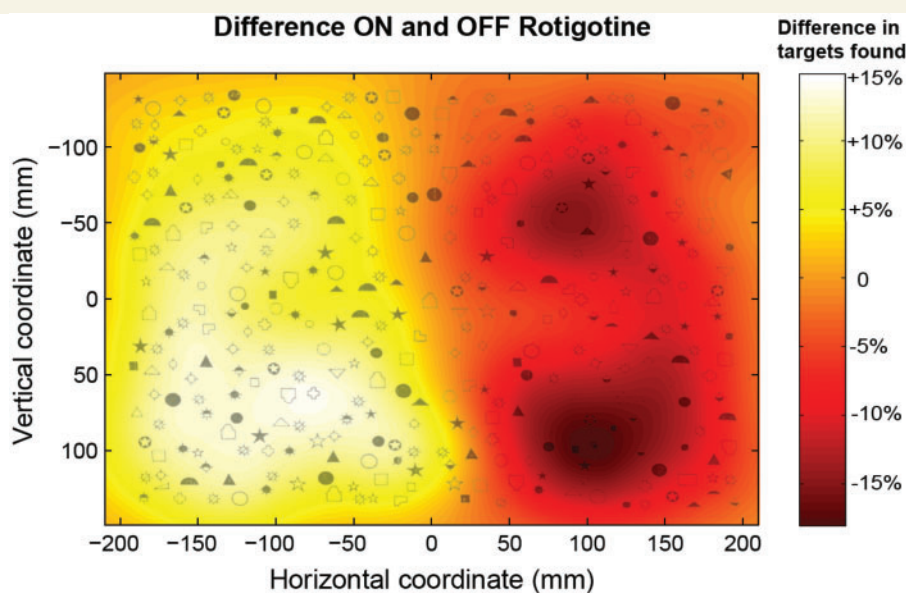


Figure 3 Difference in performance on the Mesulam cancellation task ON and OFF rotigotine for all patients. A heatmap of the difference in targets found ON and OFF treatment for the entire patient group is overlaid on a Mesulam test sheet. Colour represents difference ON and OFF treatment in the number of targets found per session per patient at each target location. Treatment with rotigotine was associated with a significant increase in the number of targets identified on the left side. A decrease in the number of targets found during treatment in a smaller area on the right-hand side was not statistically significant.

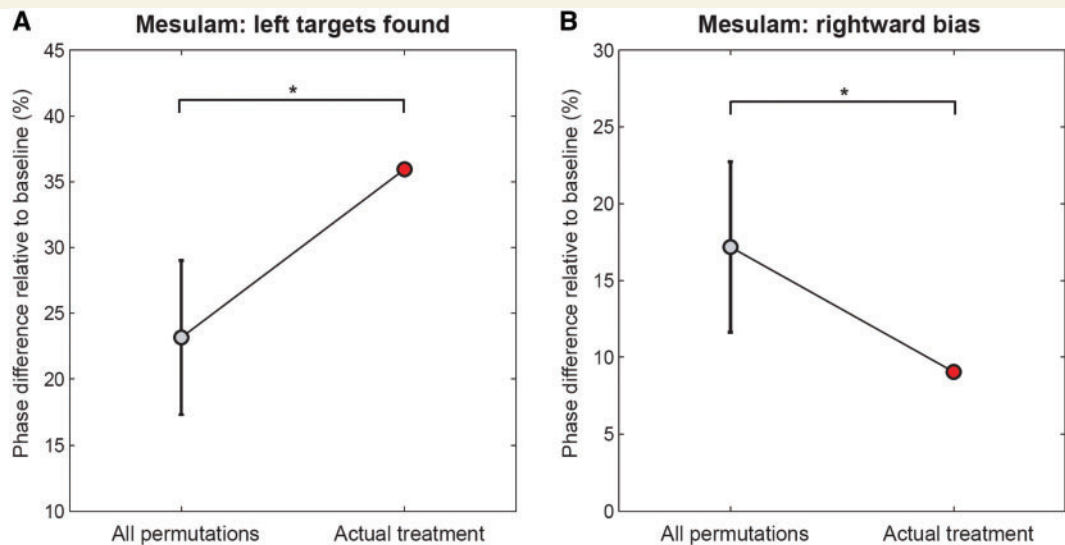


Figure 4 Overall effect of rotigotine treatment on Mesulam cancellation task. Y-axes represent per cent difference between performance ON treatment (Phase B) and OFF treatment (average of Phases A1 and A2), relative to OFF treatment baseline. The actual differences ON and OFF treatment (in red) are compared with the average (\pm average SEM) of differences between Phases B and the average of A1 and A2 produced by all possible combinations of the data (in grey). $*P < 0.05$. (A) The difference ON and OFF treatment in the number of targets found on the left side relative to baseline was higher in the actual treatment allocation, compared with all other possible permutations. (B) There was significantly less rightward bias in the location of the targets found during treatment with rotigotine, in comparison to differences produced by all possible permutations of the data.

permutation analysis for each patient on the Mesulam task are illustrated in Fig. 6A and B for difference in the targets found on the left side (positive values in Fig. 6A indicate improvement) and alteration in spatial bias (leftward shifts in Fig. 6B denote improvement). Red circles demonstrate ON versus OFF treatment values (i.e. the actual treatment allocation data); grey lines show the range of such values for all possible permutations of the data in that patient and grey squares indicate the mean difference derived from all possible permutations of the data. Note that the ranges for each patient vary depending upon the variability of performance measures across all permutations (shufflings) of the data set in each patient.

Some patients showed a strong effect ON drug when compared with all possible permutations of the data (red circles well to the right of the range). Conversely, in other patients the differences in the actual treatment allocation were comparable to differences in other arrangements of the data, suggesting little effect of rotigotine on performance. Moreover, as shown in Fig. 6C, the effect of rotigotine did not appear to depend on baseline performance (degree of neglect), as a beneficial effect—or otherwise—was observed across a range of baseline performance. Additionally, the effect of rotigotine did not appear to be affected by age, as there was no significant difference between age of patients who responded best to treatment (Patients 1, 3, 9, 11 and 13) and those who showed poor response [$t(14) = -0.61$; $P = 0.55$]. Nor was there any relationship to adverse effects: at least two patients who showed benefit in visual search had no adverse effects ON rotigotine, and overall the adverse effect profile was comparable between patients who responded to rotigotine and those who did not (Table 2). Analysis of lesions of patients who showed a

response versus those who did not is provided in the online Supplementary material, but we would urge caution in interpreting these data, given the relatively small sample size.

Unlike the results for the Mesulam cancellation task, there were no significant positive or negative effects of treatment with rotigotine on bells cancellation or touch screen visual search tasks at the group or subgroups level. Similarly, we did not observe any significant alteration in line bisection performance, although we note that mean pretreatment baseline performance in line bisection in our sample was relatively close to normal (mean rightward deviation: 4.5 mm).

One possible mechanism by which rotigotine might have exerted its positive effect on visual search in the Mesulam cancellation task could be by enhancing spatial working memory. We quantified working memory performance using a vertical analogue of the Corsi blocks task and also by measuring the number of revisits of previously identified targets in the touch screen visual search task. There was no evidence from either measure that treatment was associated with improvement of spatial working memory. Thus, performance on the vertical Corsi task did not improve on rotigotine (spatial memory span for the entire group: $P = 0.377$; minimal prefrontal subgroup: $P = 0.548$; extensive prefrontal subgroup: $P = 0.287$), and treatment was not associated with a significant decrease in the number of revisits in the touch screen task (entire group: $P = 0.821$; minimal prefrontal subgroup: $P = 0.489$; extensive prefrontal subgroup: $P = 0.909$).

An alternative hypothesis is that the effect of rotigotine on visual search might be due to an improvement of selective attention through D_1 receptor modulation (Noudoost and Moore,

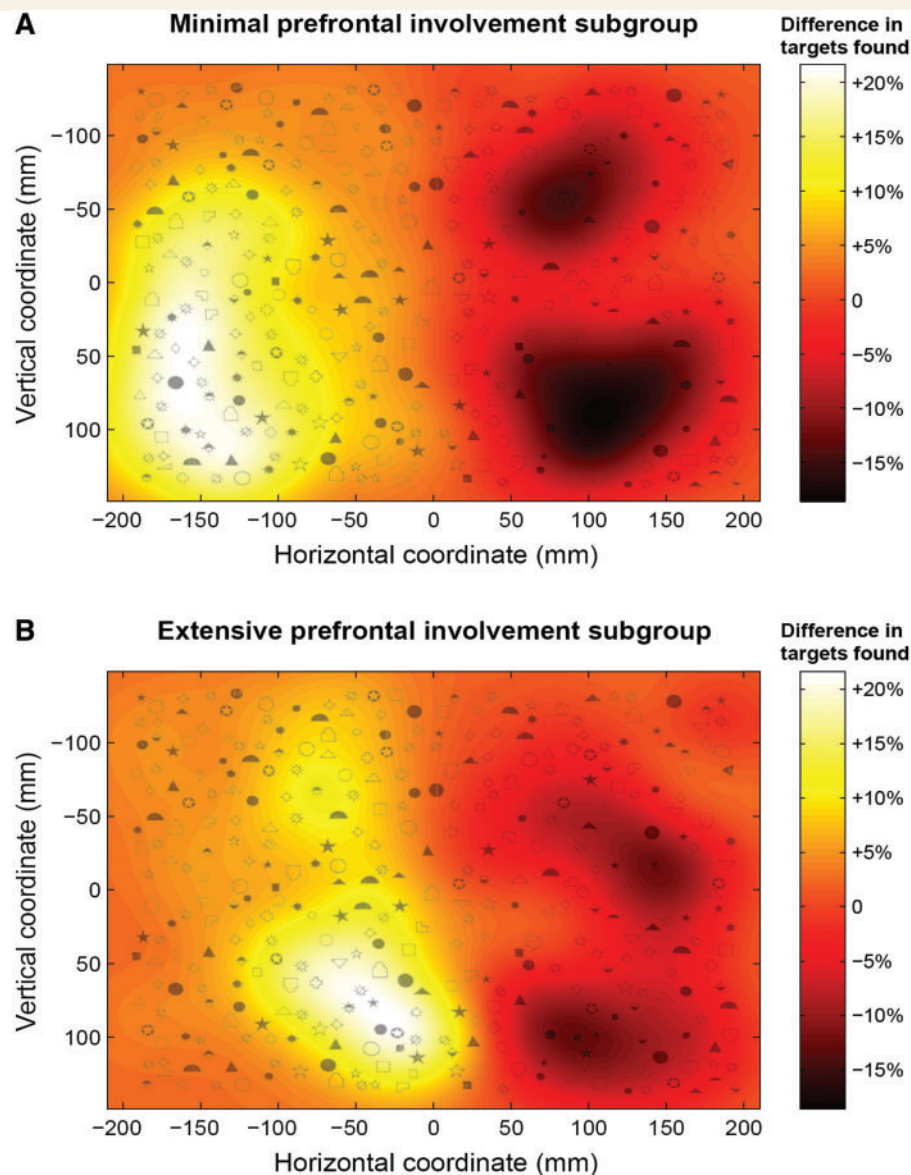


Figure 5 Difference in Mesulam task performance ON and OFF rotigotine in the two subgroups defined according to involvement of prefrontal cortex in the stroke lesion. (A) In the subgroup with minimal prefrontal involvement, the number of targets found on the left side increased significantly on treatment. (B) Patients with extensive prefrontal involvement showed a significant reduction in rightward spatial bias during treatment.

2011). We used a specific task to directly quantify attention (visual salience and vigilance task). In this task, we measured the ratio of reaction times to respond to high salience targets versus low salience targets presented on the left or right of fixation. At the group level, there was a significant increase in this ratio for left-sided targets during treatment, in comparison to the pretreatment baseline ($P = 0.03$, Fig. 7). This effect was of only marginal significance when comparing treatment to the post-treatment baseline alone ($P = 0.068$), or to the average of both OFF treatment phases ($P = 0.063$).

In the extensive prefrontal subgroup, treatment with rotigotine was associated with an increase in reaction time ratio to respond to salient/non-salient targets. This was when compared with the

pretreatment baseline or to the average of both treatment phases, both for left-sided targets ($P = 0.016$ and $P = 0.039$, respectively) and overall for both left- and right-sided targets (comparison with pretreatment phase: $P = 0.008$, and with OFF treatment average: $P = 0.008$). Conversely, in the minimal prefrontal subgroup, the effect of rotigotine on the same measure of selective attention was not significant (left-sided targets, comparison with OFF treatment average: $P = 0.113$), even though at baseline reaction times ratios were not significantly different between the two patient subgroups ($P = 0.537$). Therefore, treatment with rotigotine might be associated with a modulation of selective attention in neglect, especially in patients with extensive damage in the prefrontal cortex.

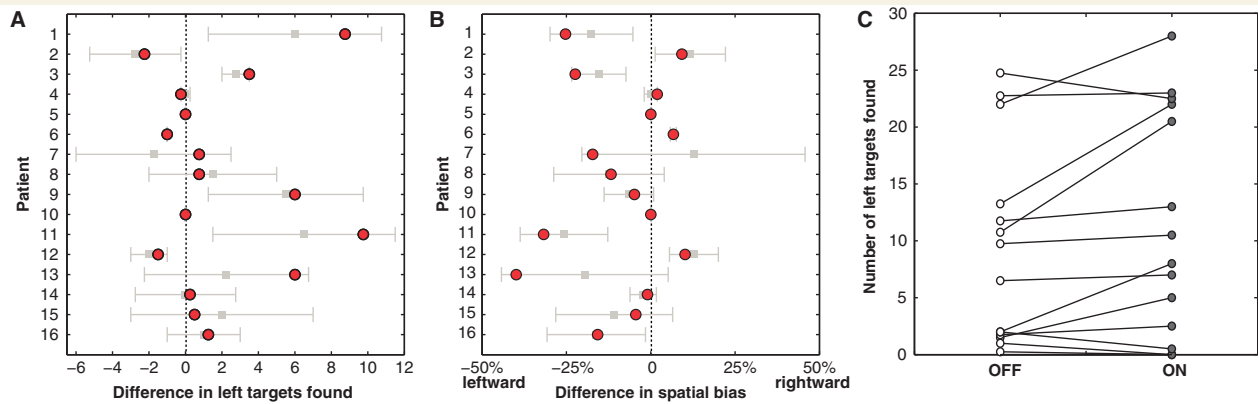
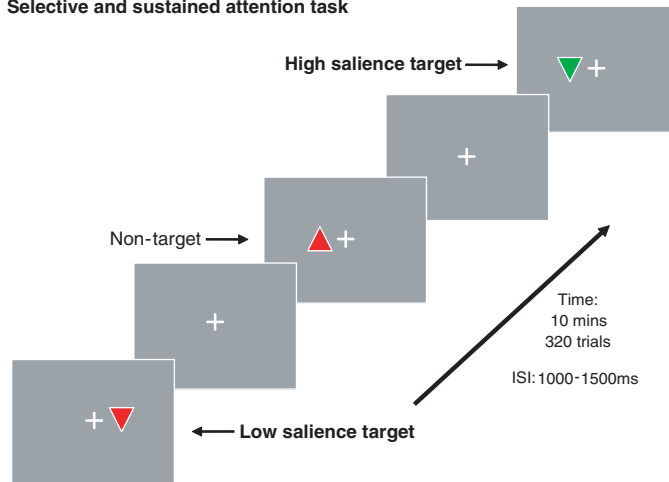


Figure 6 Mesulam task performance ON and OFF rotigotine in individual patients. Response to rotigotine was variable, across patients (presented in the same order as in Table 1). (A) Difference in left targets found ON versus OFF treatment. Red circles represent the actual difference in performance ON and OFF rotigotine for each individual. Grey squares denote the mean difference derived from all possible permutations of the data while the error bars show the range of values of such means for all possible permutations. Red circles situated on the right of error bars signify a greater number of targets found while ON the drug when compared with all possible allocations of treatment and placebo. (B) Difference in spatial bias ON versus OFF treatment. Here leftward shifts in search are displayed on the left. Red circles on the left of error bars signify less rightward bias in the location of the targets found while on the drug when compared with all possible allocations of treatment and placebo. (C) Difference in number of targets found on left as a function of number of targets found OFF treatment. Improvements occurred both in patients with poor performance at baseline (small number of targets found on the left side) and in those with good baseline performance.

A Selective and sustained attention task



B RT salient / RT non-salient

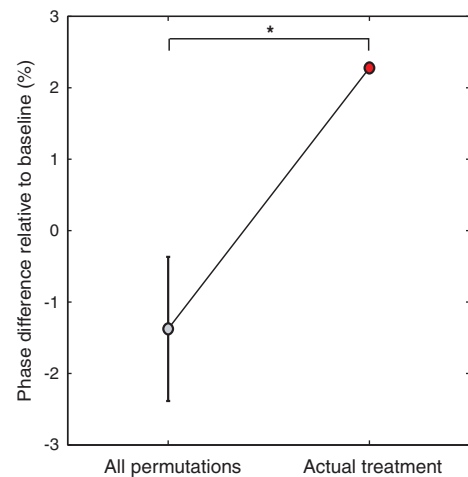


Figure 7 (A) Selective and sustained attention task. Participants detected targets (inverted triangles) among sequences of distractors (upright triangles) randomly presented to the ipsilesional and contralesional visual fields. Targets could be of the same colour as the distractors (red—low visual salience) or of a different colour (green—high visual salience). Participants were asked to respond with a button press as soon as they saw a target of any type. (B) Effect of rotigotine treatment on selective attention for left-sided targets. Y-axes represent per cent difference between performance ON (Phase B) and pretreatment (Phase A1), relative to pretreatment baseline. The actual differences ON and pretreatment (in red) are compared with the average (\pm average SEM) of difference between Phases B and A1 produced by all possible combinations of the data (in grey). The difference ON and pretreatment in the ratio of the reaction time (RT) to salient targets over non-salient targets on the left side relative to baseline was higher in the actual treatment allocation, when compared with all possible permutations. $*P = 0.03$. ISI = inter-stimulus interval.

A further possibility could be that rotigotine improved visual search by enhancing non-selective sustained attention, a cognitive ability that can be impaired in neglect (Hjaltason *et al.*, 1996; Robertson *et al.*, 1997b). To control for this possibility, we used

as a measure of sustained attention and alertness across time the difference in performance between the first and the second half of each session of the visual salience and vigilance task. However, rotigotine was not associated with a change in this measure in

either the entire group ($P = 0.697$) or the two patient subgroups (minimal prefrontal: $P = 0.555$ and extensive prefrontal: $P = 0.727$).

Finally, treatment with rotigotine was not associated with any significant improvement or worsening in any of the motor tasks in the patient group as a whole, or in either of the patient subgroups. Thus, in this sample, there was no evidence of a positive effect on motor control after stroke using rotigotine.

Discussion

We performed a randomized, double-blind, placebo-controlled study of the dopamine agonist rotigotine in patients with hemispatial neglect and left-sided motor weakness following right-hemisphere stroke. A randomized ABA design was used, with each patient assessed in three phases: before, during and after treatment with rotigotine, for a total of 20 consecutive sessions. The exact number of sessions within each phase was randomized and the difference ON and OFF rotigotine in the actual treatment allocation was compared with the differences derived from all possible permutations of phase durations computed from each patient's data. This rigorous methodology enabled us to assess the effectiveness of rotigotine without the need for an extensive sample size (Ferron and Onghena, 1996; Edgington and Onghena, 2007). Nevertheless, our relatively small sample of 16 patients is still the largest that has been reported to date in any study on drug treatment in neglect following stroke (Fleet *et al.*, 1987; Geminiani *et al.*, 1998; Grujic *et al.*, 1998; Hurford *et al.*, 1998; Barrett *et al.*, 1999; Mukand *et al.*, 2001; Malhotra *et al.*, 2006; Buxbaum *et al.*, 2007; Vossel *et al.*, 2010).

Treatment with rotigotine was associated with a significant increase in number of targets identified on the left and a decrease in the pathological rightward spatial bias on the Mesulam shape cancellation task, a visual search test widely used to assess neglect in clinical practice. Of note, rotigotine was associated with a 12.8% increase in number of targets found on the left in the actual treatment allocation in comparison to all possible permutations of the data. However, there was considerable variation across individuals and it is, as yet, unclear which patients are most likely to benefit. Importantly, response did not appear to depend upon baseline degree of neglect or extent of prefrontal involvement.

Although the positive effect of rotigotine was moderate, it is potentially important, bearing in mind, that our study design investigated short-term treatment over only 7–11 days. The result compares favourably with the effects of most other neuro-modulatory agents established in the clinical treatment of cognitive deficits, which overall are typically very modest (Husain and Mehta, 2011), e.g. of the order of 3% over several months for cholinesterase inhibitors used for the treatment of dementia (Erkinjuntti *et al.*, 2002). Of course, the clinical use of such treatments has been challenged on the basis of their small overall effect sizes, but it is also apparent that there is considerable heterogeneity of response, with some patients demonstrating very strong effects while others show none.

Although the relatively small sample size of our own study does not allow for a systematic data-driven investigation of the possible

determinants of between-subject variability, larger studies in the future might identify possible predictors of treatment response, which could permit patient selection for targeted treatment. For example, our study included patients with a wide range of time since stroke and did not differentiate between patients with an ischaemic or haemorrhagic aetiology. Future investigations with larger samples might attempt to control for such variables. In addition, it would be crucial to examine the impact of the drug on everyday life, using functional outcome measures: activities of daily living and functional measures of neglect (Azouvi *et al.*, 2003).

It should be noted that we did not identify any significant effects of rotigotine on two other visual search tasks (bells cancellation and touch screen cancellation tests). Possible reasons for this discrepancy might relate to display parameters in these tasks. Specifically, in the bells cancellation task there is a smaller number of targets and distractors than in the Mesulam test (34 versus 60 targets; 278 versus 311 distractors), and in the touch screen visual search task the targets and distractors were presented in a smaller area. These parameters may render the bells and touch screen visual search tests less sensitive than the Mesulam shape cancellation task (Kaplan *et al.*, 1991), making the effects of treatment less discernible. Rightward deviation in line bisection also did not improve significantly on treatment. Given that performance in the pre-treatment baseline phase was already close to normal in our patient group, this may represent a ceiling effect. Response to treatment did not appear to depend simply on task difficulty or complexity, as rotigotine had a significant improvement on the Mesulam task, while there was no significant effect of the drug in arguably both simpler (line bisection, Bells cancellation) and more complex tasks (touch screen cancellation).

The current study was designed not only to assess the effectiveness of rotigotine in ameliorating spatial bias in neglect but also to identify possible cognitive mechanisms that may mediate this effect. Based on existing evidence on the role of D_1 dopamine receptor activity in spatial working memory (Funahashi and Kubota, 1994; Castner *et al.*, 2000; Castner and Goldman-Rakic, 2004), we hypothesized that rotigotine might improve performance on cancellation tasks by enhancing working memory for the location of previously cancelled targets, and therefore diminishing 'revisiting' of previously explored locations (Mannan *et al.*, 2005; Parton *et al.*, 2006). However, rotigotine was not associated with improvement of spatial working memory, indexed either indirectly, by measuring the number of revisits in the touch screen cancellation task (Parton *et al.*, 2006), or directly, using a vertical variant of the Corsi spatial memory task (Malhotra *et al.*, 2005).

An alternative mechanism that may explain the positive effects of rotigotine in the Mesulam cancellation task would consist of a direct enhancement of selective attention by increased dopaminergic activity. This hypothesis is compatible with recent evidence that local administration of a D_1 dopamine receptor modulator in the monkey frontal eye field alters selectivity and reliability of eye movements to visual targets and modulates neuronal activity in visual area V4 in the same way that selective voluntary attention does (Noudoost and Moore, 2011). If this were the case also in humans with visual neglect, one might expect the drug to induce more effective allocation of voluntary attention to task-relevant

target stimuli and, correspondingly, less involuntary attentional capture by the task-irrelevant (but visually salient) distractors, therefore making identification of correct items more effective.

Interestingly, the results from our combined visual salience and vigilance task suggest that ON rotigotine responses to less salient (but equally task-relevant) targets became faster on the left, relative to more salient ones. This might be in keeping with more effective voluntary allocation of selective attention to task-relevant visual targets and less involuntary attentional capture, driven by stimulus salience, on rotigotine. Therefore, it is possible that rotigotine improved performance on the Mesulam search task by enhancing selective attention to targets, while reducing involuntary attentional capture by distractors. This result is consistent with the known role of dopamine in mediating attention switching and arousal to behaviourally relevant stimuli and modulating goal-directed behaviour (Bromberg-Martin *et al.*, 2010; Cools, 2011).

Note that if the positive effects of rotigotine on neglect were due simply to non-specific, motivational processes, one would expect a general improvement across multiple tasks. Instead, we observed specific effects on the Mesulam search task and on our selective and sustained attention task. The results from the latter paradigm are particularly useful as they show that rotigotine had a specific effect in improving selective attention to task-relevant targets, over detection of salient, but task-irrelevant targets. Non-selective, sustained attention can be impaired in neglect and has been shown to correlate with neglect severity (Hjaltason *et al.*, 1996; Robertson *et al.*, 1997b). Importantly, we did not find any effect on sustained attention on this task, which would be expected if the effects of rotigotine were to improve non-specific arousal and motivation. Thus, the effects of treatment seem to be highly specific, improving selective, voluntary attention rather than enhancing sustained, non-selective attention across time.

We have hypothesized that modulation of D₁ receptor activity might provide a possible mechanism by which visual search in neglect can be ameliorated through enhancement of working memory or selective attention. In comparison to other dopamine agonists approved for clinical use, rotigotine has a relatively high D₁ receptor affinity. However, it should be noted that it has an even higher affinity to D₂ and D₃ receptors (Belluzzi *et al.*, 1994; Jenner, 2005; Naidu and Chaudhuri, 2007). Therefore, the effect of rotigotine on visual search in the patients we studied might also have been mediated, at least in part, by D₂ and/or D₃ agonist activity.

According to our original hypothesis, the effects of rotigotine in neglect would be mediated by increased dopaminergic activity in the right prefrontal cortex. In that case, we would expect to find benefit from treatment only in patients with relative preservation of right prefrontal cortex. However, we demonstrated that rotigotine was associated with significant improvement on the Mesulam shape cancellation task in both the minimal and the extensive prefrontal involvement subgroup. This suggests that integrity of the right prefrontal cortex is not critical in determining response to rotigotine, at least in the sample of patients we have assessed in this study. An alternative hypothesis could be that rotigotine modulates the activity in intact frontoparietal or fronto-occipital networks (Bartolomeo *et al.*, 2007; Doricchi

et al., 2008; Urbanski *et al.*, 2008; Vuilleumier *et al.*, 2008), either in the lesioned or in the contralesional hemisphere, effectively 'rebalancing' pathological overactivity in structurally intact brain networks that may contribute to lateralized attentional imbalance in neglect (Corbetta *et al.*, 2005).

In a prospective study, L-DOPA as an adjuvant of physiotherapy has been demonstrated to improve motor function in stroke patients with unilateral weakness (Scheidtmann *et al.*, 2001). We did not find any significant effect of rotigotine treatment on motor performance. However, the current study was not designed to assess drug effects prospectively, and the amount of physiotherapy received by each patient was not controlled, therefore although we did not find an effect of rotigotine alone on motor performance, it remains an open question whether this drug may benefit motor rehabilitation when used as adjuvant of physiotherapy. Indeed, given the well-recognized role of dopamine in complex reinforcement learning (Dayan and Balleine, 2002; Wise, 2004), a possible synergistic role of dopamine agonists in novel rehabilitative approaches that aim to improve spatial awareness in neglect (Parton *et al.*, 2004) also presents itself as an important question for future research.

This study was the first successful randomized, double-blind placebo controlled study of the dopamine agonist rotigotine in a group of stroke patients with hemispatial neglect and unilateral weakness. Rotigotine was reasonably well tolerated in this setting and was associated with significant improvement in one visual search task. Placebo-controlled N-of-1 randomized design, such as the one used here, provides a useful means to test proof-of-principle for potential new therapies. However, larger trials, including measures of functional efficacy, will be needed to confirm whether this treatment may be practical for widespread clinical use in hemispatial neglect following stroke.

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Supplementary material

Supplementary material is available at *Brain* online.

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