Rotigotine in hemispatial neglect following stroke: a double-blind randomised trial

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Summary

Background: Hemispatial neglect following right hemisphere stroke is a common and disabling disorder, for which there is currently no effective treatment. Dopamine agonists have been shown to play a role in working memory and selective attention, two core cognitive components of neglect. We aimed to investigate whether the dopamine agonist rotigotine would have a beneficial effect on hemispatial neglect in chronic stroke patients.

Methods: A novel double-blind, randomised, placebo controlled ABA design was employed, in which each patient was assessed intensively over 20 testing sessions, in three phases: before treatment (A1), on transdermal rotigotine (B), and after treatment discontinuation (A2), with the exact duration of each phase randomised within limits and each participant receiving placebo when they were not receiving rotigotine during a pre-defined part of the trial. Outcome measures included spatial bias in cancellation (visual search) tasks and line bisection, as well as visual working memory, selective attention and sustained attention. Motor performance was also assessed.

Findings: 16 patients were recruited. All patients completed the trial. Spatial bias in the Mesulam shape cancellation task improved significantly while on rotigotine (spatial bias relative to baseline reduced by 8.1%, P=0.016). This improvement in visual search was associated with an enhancement in selective attention but not in working memory or sustained attention. Rotigotine was not associated with improvement in motor performance. The main adverse events while on rotigotine or placebo were fatigue (four [25%] *vs* one [6%]), topical skin reaction at the site of the patch (one [6%] *vs* 0) and transient digestive disorders including nausea (five [31%] *vs* 0), vomiting (one [6%] *vs* 0) and diarrhoea (two [13%] *vs* 0).

Interpretation: In patients with hemispatial neglect following stroke, rotigotine was associated with significant improvement in performance on a visual search and a selective attention task.

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Conflict of interest: None

Role of authors: NG, YM, BM performed testing for the trial and were involved in data entry. The trial statistician, EK, and NG performed statistical analyses. NG and MH wrote the first drafts; all authors (excluding EK) were involved in patient recruitment and commenting on manuscript drafts. MH and NW applied for funding for this study.

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Introduction

Cognitive impairment following stroke represents a major clinical challenge (1). One of the most commonly encountered disorders is hemispatial neglect, a syndrome that is most pronounced and long-lasting after right-hemisphere stroke, involving up to two thirds of such patients acutely (2). These individuals demonstrate a striking failure to respond to people or objects to their left. Although enduring neglect is recognised as a poor prognostic indicator for functional independence (3), it is underdiagnosed (4) and there is no established drug or rehabilitative therapy.

Neglect consists of several component deficits (5-9), with different patients suffering different combinations of cognitive impairment (10), including aspects of selective and sustained attention. A potentially important component demonstrated in recent studies is a deficit in remembering spatial locations over brief periods of time (11). Landmark studies in monkeys have shown that such spatial working memory is modulated by prefrontal dopamine D_1 receptors (12). Selective D_1 agonists can improve working memory in elderly monkeys (13), or reverse experimentally-induced spatial working memory deficits (14). In healthy humans too, D_1 agonists can facilitate spatial working memory (15). More recently, frontal D_1 agonist activity has been shown to have long-range, modulatory effects on posterior visual areas subserving selective attention (16). Dopaminergic networks have also been implicated in the process of alerting (17).

These findings raise the possibility of using a D_1 agonist to ameliorate neglect following stroke. There have been few previous attempts to assess dopaminergic modulation in neglect: most studies have been open-label with the largest trial assessing only four

patients, and the results have been mixed (18-23). Here, we report on a double-blind, randomised, placebo controlled trial of the dopamine agonist rotigotine, administered as a transdermal patch. In contrast to substances tested in previous studies, we used rotigotine, which has relatively high D_1 receptor affinity. Our primary objective was to evaluate whether the drug improves neglect and its cognitive components, including spatial working memory, selective and sustained attention. A further aim was to assess the effects of rotigotine on motor performance, because levodopa has been reported to have positive effects on post-stroke motor deficits (24).

A novel replicated ABA double-blind, placebo-controlled N-of-1 randomised design was used (25), allowing us to evaluate the effectiveness of an intervention in small sample sizes. Each patient's performance was measured in three phases (figure 1): before treatment (**phase A1**), while receiving rotigotine (**phase B**) and after discontinuation of the drug (**phase A2**). Crucially, the exact duration of each phase was randomised across patients: unlike traditional randomised controlled trials (RCTs), all patients received placebo and drug at different stages of the trial, with the exact time at which drug is started and duration of treatment randomised across individuals. This design requires intensive, repeated testing of participants but has the advantage of potentially providing useful results in small numbers of participants (panel 1 gives further details).

Panel 1: Replicated randomised N-of-1 design

Replicated randomised N-of-1 designs (25) such as the one used here were originally developed by Fisher for intervention studies (26) but were difficult to conduct on a large scale because they require substantial computing power. Modern day computers make such demands far less problematic, and replicated randomised 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. Randomisation or permutation tests are used for analysis of these designs.

Importantly, randomisation tests are distribution-free. They are based simply on rearrangements of raw scores. They compare a computed statistic (e.g., 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 it is by chance that a difference in means was as large as the observed difference between two conditions, e.g., treatment vs. no treatment.

In the design used here (**figure 1**) we can compare the difference in mean scores between two phases of the trial, e.g., **Phase A1** prior to treatment and **Phase B** on drug. Suppose the difference in mean scores between these two phases for the patient who underwent the protocol shown in **figure 1A** is *Z*. Randomisation tests consider all other possible rearrangements of the data *for this patient*, within the constraints of the trial design (shown in **figure 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 and B period is computed. Then the probability that other possible rearrangements of the dataset result in a value as large as, or larger than Z, is calculated.

In other words, this method 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 that might have been possible (with the acquired data set) if the actual treatment period had been different. Thus we calculate what the means would have been for phase A1 and phase B if the patient had started the drug a day earlier, or a day later or even two days later; or if the time on the drug had been longer or shorter than it actually was, within the constraints of the trial design (in our case there were 15 such permutations). Then we compare the differences in means for all these permutations with the actual, observed difference in means between phase A1 and phase B. 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 randomised to receiving treatment or no treatment as in conventional RCTs. The patient here is their own control. Individual p-values are combined to obtain a p-value for the whole patient group.

Methods

Patients

Individuals >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. Left hemispatial neglect was defined as a significant deficit in finding leftward targets on standard cancellation or visual search tasks, using established criteria (51-53). 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 ≤ 4+ on the MRC scale. Patients were eligible only if stroke onset was at least 9 days before the first assessment session.

Exclusion criteria were:

- A pre-existing neurological condition that would confound cognitive or motor assessments
- Acute concomitant illness
- Systolic blood pressure <120 mmHg and / or diastolic <70 mmHg
- Exposure to any other investigational drug within 30 days of enrolment
- Presence of clinically significant drug or alcohol abuse within previous 6 months
- Pregnancy and breast feeding.

All patients provided written informed consent. The study protocol and all relevant documents and procedures were approved by the National Research Ethics Service (NRES) and the Medicines and Healthcare products Regulatory Agency (MHRA).

According to our hypothesis, the major target of rotigotine for cognitive effects is likely to be dopamine D_1 receptors in prefrontal cortex. Patients were therefore stratified into two subgroups according to the extent of prefrontal cortical involvement. An established lesion mapping technique (27) was employed, using MRIcron software, (www.cabiatl.com/mricro). The percentage of prefrontal involvement was quantified for each patient, by comparing their normalised brain lesion to a prefrontal template, defined using the PickAtlas SPM toolbox (http://fmri.wfubmc.edu/software/PickAtlas).

Randomisation and masking

A double-blind, placebo-controlled 'ABA' randomised design was used consisting of three consecutive phases (figure 1):

- Baseline pre-treatment phase (A1)
- Treatment with rotigotine transdermal patches (phase B)
- Post-treatment phase (A2)

The duration of each phase was randomised 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.

Phase A1 started on session 1 and its duration was randomised (across individuals) to between 5-9 days. Observations during this phase established the baseline

performance. **Phase B**, when rotigotine was administered, could commence on day 6 to 10, and its duration was a minimum of 7 and a maximum of 11 sessions. Finally, **phase A2**, when patients were assessed after the discontinuation of rotigotine, was randomised to begin between sessions 13-17, and it lasted for the remaining 4-8 sessions. For the purpose of placebo control, all patients received a placebo patch in the period between sessions 6-16, 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.

As an example, the randomisation profile of one of the participants is presented in figure 1a. In this case, the patient had 6 baseline assessments, followed by 8 days on rotigotine (sessions 7-14) and 6 follow-up assessments after discontinuation of the drug. In the figure the yellow shading shows the minimum number of sessions in phases A1 and A2, while red denotes the treatment phase (B). Orange depicts any additional sessions in phases A1 and A2 when the patient received placebo patches. Some other possible permutations of pre-treatment, treatment and post-treatment phases within the constraints of the design are shown in figure 1b. In total, there were 15 possible permutations.

Procedures

Each patient participated in 20 consecutive assessment sessions. The first 17 sessions were performed daily. The final 3 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 (28), and with three visual search tasks, each with a 2 minute time limit: Mesulam shape cancellation and bells cancellation task, performed on A3 sheets, and a visual search task performed on a touchscreen (18'' diagonal), in which no visible markings were left at the location of the cancelled targets (29). Spatial working memory was measured with a vertical analogue of the Corsi spatial span test (11), and also using the rate of revisiting of previously cancelled targets obtained from the touchscreen visual search task (29).

Selective attention and sustained attention were assessed using a visual salience and vigilance task, previously used in patients with prefrontal lesions (30): participants detect targets (inverted triangles) among sequences of distractors (upright triangles) randomly presented in ipsilesional and contralesional visual fields, responding to targets with a speeded button press (figure 6a). Targets could be of the same colour as distractors (low visual salience) or of a different colour (high salience). As a measure of selective attention, we used ratio of reaction time (RT) to high salience targets over RT to low salience targets. Furthermore, using this task, we quantified sustained attention *over time*, by measuring the difference in RT and % correct responses between the first and the second half of each session.

Motor performance was evaluated in all patients using the Motricity Index and with grip and pinch dynamometry. Where the patient's level of weakness permitted, motor performance was also assessed using the 9-hole peg test, box and blocks test and timed 10 metre walk.

During the treatment phase, a rotigotine 9.0 mg skin patch (4mg/24hr transdermal absorption) was applied daily by the investigator. Because rotigotine takes up to 24 hours 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 on sessions 5-15. Therefore, either placebo or rotigotine was in place during behavioural testing on 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 10mg orally three times daily from sessions 1 to 16. As domperidone does not penetrate the blood-brain barrier, it should not interfere with the central response to rotigotine. 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 randomised N-of-1 design (25) 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 consisting of 17 consecutive daily assessments, followed by 3 weekly ones. This design methodology, sometimes also referred to as permutation testing, makes no assumptions about the underlying distribution of the data (31), and has been shown to be particularly robust

for studies with small sample sizes (32).

For each patient and each outcome measure, we computed three statistics:

1. Difference of median observation of phase B from median of phase A1 (B-A1),
2. Difference between medians of phases B and A2 (B-A2), and
3. Difference between 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 (see fig 1). By all possible rearrangements, we mean that given the data for any individual we calculated possible medians for each phase, but now with different durations of each phase than the actual one used. In this way, we obtain *from the acquired data* a series of possible values for B-A1, B-A2 and B-Am, that might have occurred if the actual time of start and end of treatment had been different. 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 (33). 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 the trial statistician (author EK).

Role of the funding source

The sponsor had no involvement in study design, data collection, analysis, interpretation of the results, or writing of the report. The principal investigator (MH) had full access to all the data and had final responsibility for the decision to submit the report for publication. UCB Pharma provided drug and placebo patches gratis but was not involved in designing the study or its execution.

Results

16 patients fulfilling the inclusion criteria were prospectively enrolled (table 1 and figure 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, apart from patient 7 who missed one testing session (session 11, on rotigotine), for reasons unrelated to the trial.

There were no serious adverse events. Adverse effects included fatigue, mild skin irritation at the site of the patch, and gastrointestinal disturbance, including nausea, vomiting and diarrhoea (table 2). Neither treatment nor assessments were interrupted due to adverse events.

Treatment with rotigotine was associated with significant improvement in visual search, as quantified by the Mesulam shape cancellation task. As shown in figure 3, for the entire group of 16 patients, the number of targets found on the left was significantly higher while on rotigotine than in pre- and post-treatment phases averaged (P=0.012), or in the post-treatment phase alone (P=0.039). The difference on and off treatment in the number of targets found on the left 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 (figure 4a). Although the number of targets found on the right side was somewhat decreased on treatment (figure 3), the relative difference on and off treatment was only 0.7% smaller in the actual treatment allocation when compared to all possible permutations (not statistically significant; P=0.466).

Spatial bias in visual search (ratio of difference in targets found on either side to total number of targets found) also improved significantly on rotigotine when compared to the post-treatment phase (P=0.018) or to both off-treatment phases (P=0.016, figure 3). The effect size was 8.1% less rightward bias relative to baseline in the actual treatment allocation, in comparison to all possible permutations (figure 4b).

For both the minimal prefrontal involvement subgroup (0%-15% of prefrontal cortex affected, figure 2b) and extensive prefrontal subgroup (33%-55% prefrontal cortex affected, figure 2c), there was a significant benefit of rotigotine (figure 5), but for different search parameters. The number of left targets found was significantly higher on rotigotine in the minimal prefrontal subgroup (P=0.036), but 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).

There were no significant positive or negative effects of treatment with rotigotine in line bisection, bells cancellation, or touchscreen visual search tasks, at the group or subgroups level. We note that mean pre-treatment baseline performance in line bisection was relatively close to normal (average rightward deviation: 4.5mm). There was also no evidence of improvement in spatial working memory. Thus, performance on the vertical Corsi task did not improve on rotigotine (spatial memory span for 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 number of revisits on the touchscreen search task (entire group: P=0.821; minimal prefrontal

subgroup: P=0.489; extensive prefrontal subgroup: P=0.909).

On the visual selective and sustained attention task (30), for the entire group there was a significant increase in the ratio of RT to high salience vs low salience targets for left-sided targets during treatment, in comparison to pre-treatment baseline (P=0.03, figure 6). This effect was only marginal when comparing treatment to post-treatment baseline (P=0.068), or to the average of both off-treatment phases (P=0.063). For the extensive prefrontal subgroup, rotigotine was associated with similar improvement for left targets, when compared to pre-treatment baseline or to the average of both treatment phases, (P=0.016 and P=0.039, respectively). In addition, it also had a significant beneficial effect overall for *both* left and right-sided targets (comparison with pre-treatment phase: P=0.008, and with off-treatment average: P=0.008). Conversely, in the minimal prefrontal subgroup, the effect of rotigotine had no significant effect (e.g., for 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). Thus, rotigotine was associated with a modulation of selective attention in neglect, but this was far more prominent in patients with extensive damage in the prefrontal cortex.

A further possibility is that rotigotine improved visual search by enhancing non-selective sustained attention. 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; 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.

Discussion

In this double-blind, placebo controlled trial using a novel randomised ABA design, rotigotine was associated with a significant increase in the number of targets identified on the left and a decrease in the pathological rightward spatial bias on a visual cancellation task (fig 3). Of note, rotigotine was associated with a relative reduction of 8.1% in rightward bias in the actual treatment allocation in comparison to all possible permutations of the data. This effect size compares very favourably with the effects of most neuromodulatory agents used in the treatment of cognitive deficits, which overall are typically of small magnitude (34), e.g. <5% for cholinesterase inhibitors used for dementia. Moreover, trials in dementia typically report effects after several months of treatment whereas here patients were on drug for between only 7-11 days.

The current study was designed also to identify possible cognitive mechanisms which may mediate this effect. Based on existing evidence on the role of D_1 dopamine receptor activity in spatial working memory (12-15), we hypothesized that rotigotine might improve performance by enhancing this process. However, we found no such effect on spatial working memory, indexed using two different measures.

An alternative mechanism is direct enhancement of selective attention (16) which would be expected to lead to 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. Consistent with this view, the results from our combined visual salience and vigilance task (30) demonstrate that responses to *low salience (*but task-relevant*)* targets on the left became faster on rotigotine,

relative to more salient targets. An additional possibility is that rotigotine may have enhanced patients' ability to sustain attention and remain alert over time. However, there was no significant effect of treatment on the visual salience and vigilance task across time. Nor did we find any beneficial effects of rotigotine on motor performance measures.

According to our hypothesis, the effects of rotigotine in neglect are likely to have been mediated by increased D_1 activity in the right prefrontal cortex. In that case, we would expect to find benefit from treatment with rotigotine only in patients with relative preservation of the right prefrontal cortex. However, we demonstated that treatment was associated with significant improvement in a cancellation task in both minimal and extensive prefrontal involvement subgroups. 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 here. An alternative hypothesis is that rotigotine modulates activity in intact fronto-parietal or fronto-occipital networks, either in the lesioned or contralesional hemisphere, effectively "re-balancing" pathological overactivity in structurally intact brain networks, which might contribute to lateralised attentional imbalance in neglect.

This study is the first successful randomised, double-blind placebo controlled trial of the dopamine agonist rotigotine in a group of stroke patients with hemispatial neglect. Rotigotine was well tolerated in this setting, with significant reduction of leftward neglect in a visual search task over 7-11 days. These results, obtained using an innovative trial design, support the need for a larger study to evaluate the efficacy of dopamine agonists in neglect over a longer period.

Panel 2: Research in context

Systematic review

We searched PubMed for all clinical studies of dopaminergic treatment of hemispatial neglect, using the search terms "hemispatial", "neglect", and "dopamine". Additionally, we reviewed the key basic science publications on the role of dopamine agonists on attention and working memory. There were no previous clinical trials of rotigotine in neglect. We identified three small open-label studies (18,19,21), one small single-blind placebo controlled study (23) and one case report (20) of other dopamine agonists in neglect following stroke, with sample sizes of up to four patients.

Interpretation

Previous clinical evidence for the efficacy of dopamine agonists in hemispatial neglect is very limited, and there are no previous double-blind controlled trials in this setting. Conclusions from existing studies are conflicting, with both improvement and aggravation of neglect reported.

In this proof-of-concept study, we used an ABA design with phase durations randomised within limits, which gave us the possibility to assess the effects of the dopamine agonist rotigotine on neglect and unilateral weakness, in a randomised, double-blind, placebo controlled trial, without the need for a large sample size.

We found evidence of improvement in spatial bias in one visual search task, but no improvement in motor performance. Furthermore, we investigated possible cognitive mechanisms that may explain the improvement in spatial bias, and identified modulation of selective attention as the most likely mechanism.

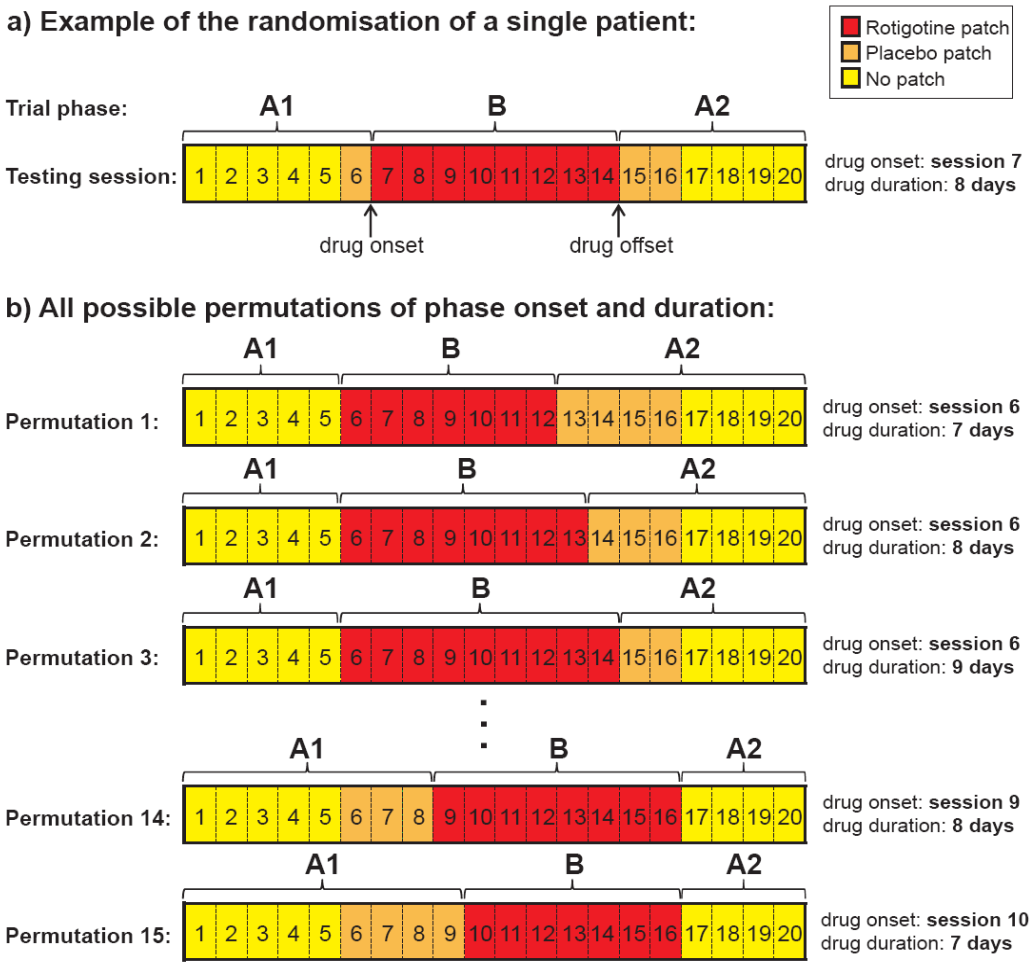

Figure 1: **Randomisation of treatment allocation and permutation tests.**

a) Randomisation profile for a single patient. In this case, the treatment phase with rotigotine (**phase B** shown in red) started on day 7, and its duration was randomised to 8 days. Therefore, the patient participated in 6 baseline assessments (**phase A1**, sessions 1-6) and 6 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 in yellow.

b) The *actual* difference in performance between treatment (B) and off-treatment phases (A1 and A2) was ranked against the differences between phases produced by *all other possible permutations* of treatment allocation, given the limits in phase onset and duration.

In this trial there were 15 possible permutations (different durations of phases A1, B and A2).

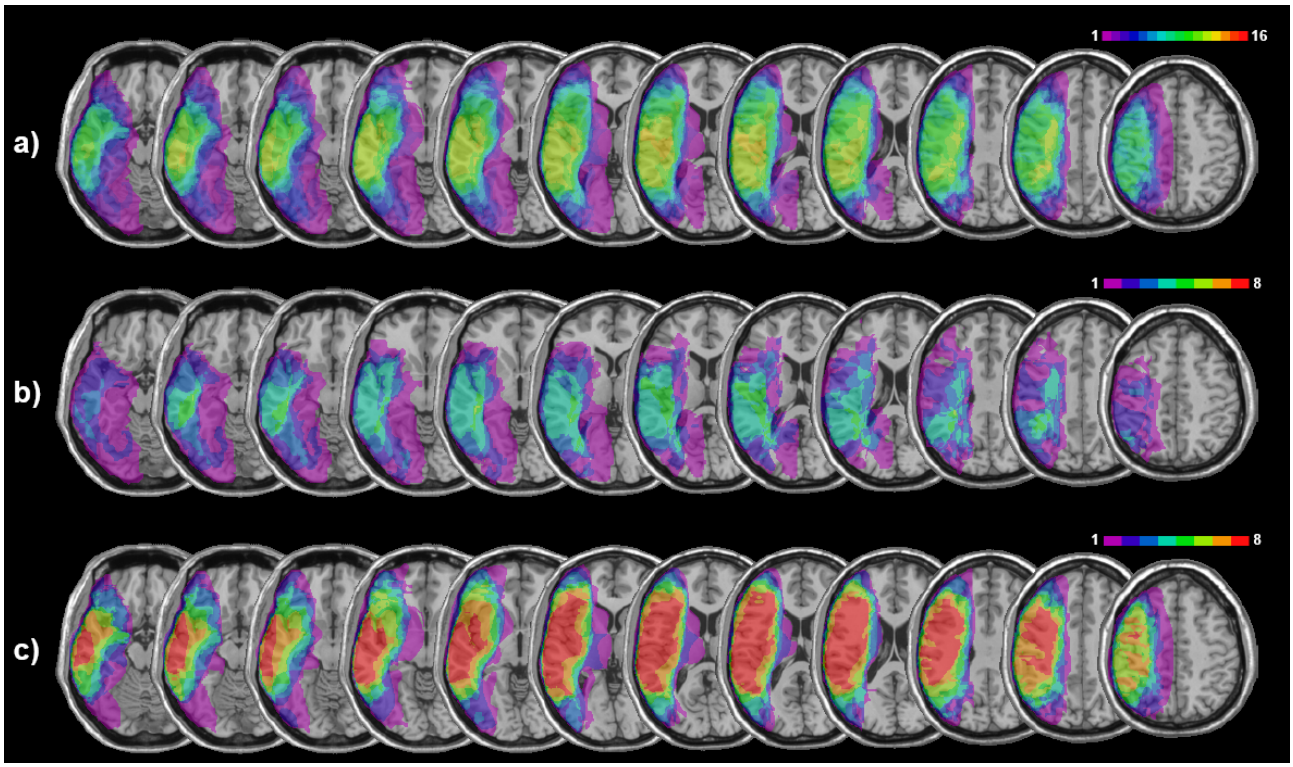

Figure 2: **Lesion overlap maps.**

Axial MRI slices of stroke lesions in **a)** the entire group of all 16 patients, **b)** the minimal prefrontal involvement subgroup (8 patients) and **c)** the extensive prefrontal involvement subgroup (8 patients). Colour values represent the number of patients in whom a given voxel was lesioned.

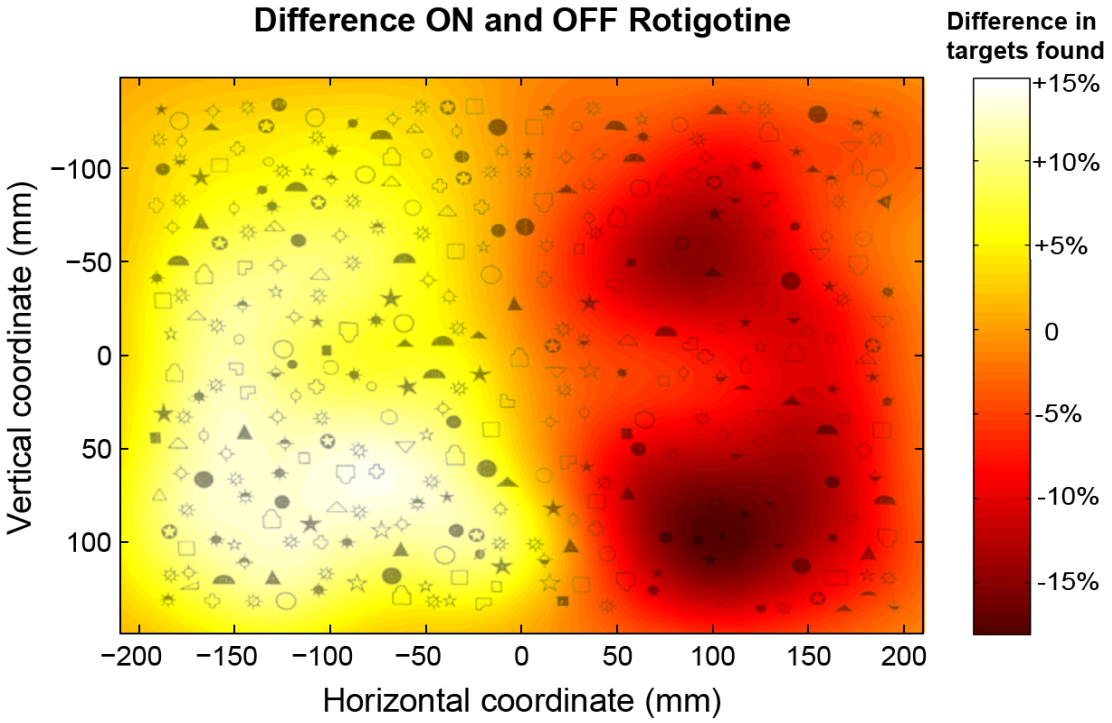

Figure 3: **Difference in performance on Mesulam visual search task on and off Rotigotine for all patients.**

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 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.

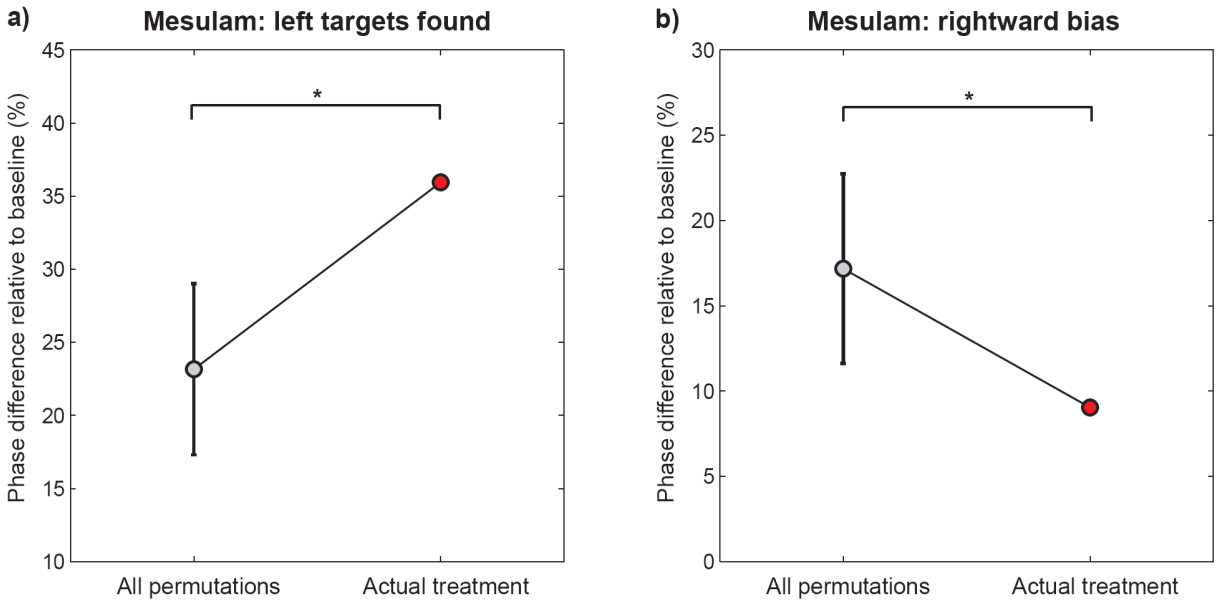

Figure 4: **Effect size of rotigotine treatment in the Mesulam task.**

Y axes represent % 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 to the average (±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, when compared to all possible permutations.

b) There was significantly less rightward lateralisation in the location of the targets found during treatment with rotigotine, in comparison to differences produced by all possible permutations of the data.

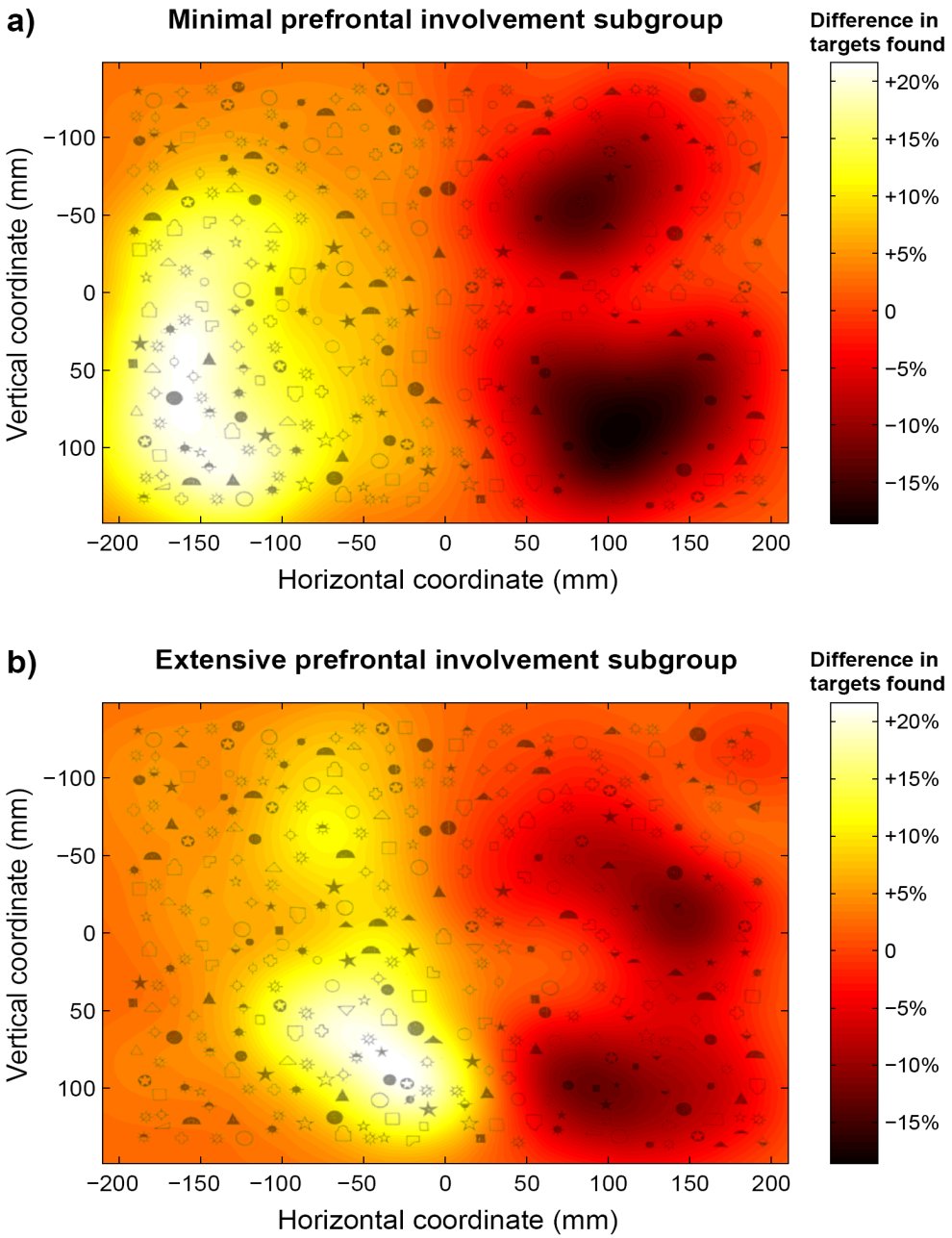

Figure 5

Figure 5: **Difference in Mesulam visual search task performance on and off rotigotine in the two subgroups defined according to prefrontal damage.**

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 significantly less rightward spatial bias during treatment.

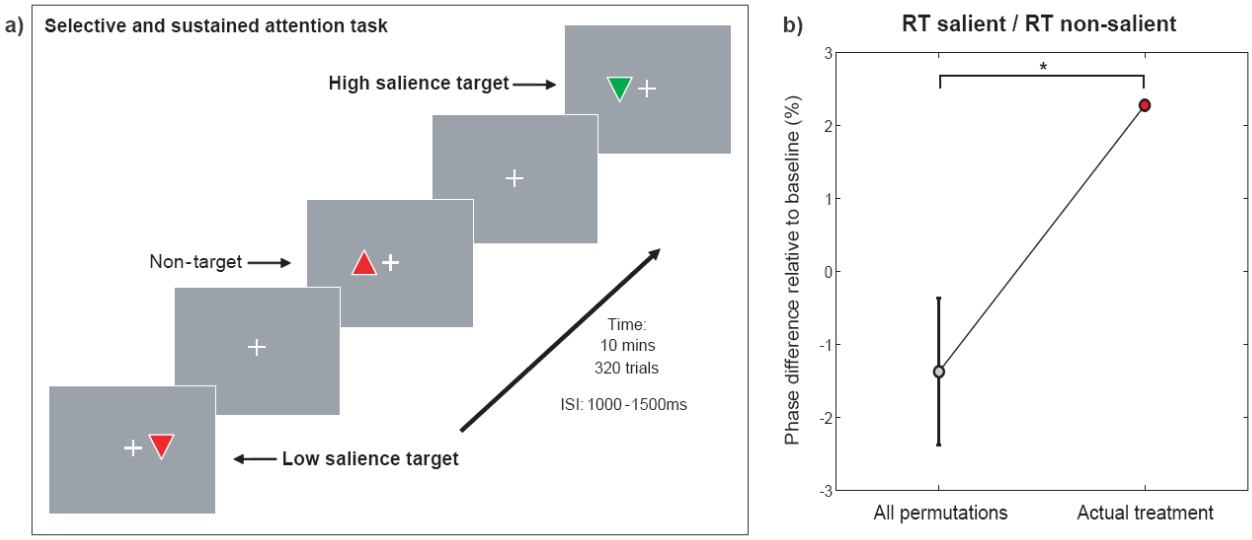

Figure 6: **Selective and sustained attention task and result for left targets.**

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 % difference between performance on (phase B) and pre-treatment (phase A1), relative to pre-treatment baseline. The actual differences on- and pre-treatment (in red) are compared to the average (±average SEM) of difference between phases B and A1 produced by all possible combinations of the data (in grey).

The difference on- and pre-treatment 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 to all possible permutations. *P=0.03.

Tables

Table 1 | Patient demographics

	Age	Gender	Handed-ness	Stroke type	Days post stroke	% prefrontal involvement	Prefrontal subgroup
P1	42	Male	Right	Ischaemic	728	39.4%	Extensive
P2	62	Male	Right	Ischaemic	70	14.6%	Minimal
P3	46	Male	Right	Ischaemic	1381	32.5%	Extensive
P4	63	Female	Right	Ischaemic	42	11.8%	Minimal
P5	58	Male	Right	Ischaemic	327	35%	Extensive
P6	66	Male	Right	Ischaemic	202	54.7%	Extensive
P7	62	Male	Right	Haemorrhagic	232	0.2%	Minimal
P8	74	Male	Right	Ischaemic	341	35.3%	Extensive
P9	53	Male	Left	Ischaemic	385	5.6%	Minimal
P10	24	Male	Right	Haemorrhagic	221	7.2%	Minimal
P11	60	Male	Right	Haemorrhagic	1990	2.4%	Minimal
P12	62	Male	Right	Ischaemic	941	33.5%	Extensive
P13	72	Female	Right	Haemorrhagic	1712	32.6%	Extensive
P14	80	Male	Right	Ischaemic	30	0%	Minimal
P15	51	Male	Right	Haemorrhagic	104	52.9%	Extensive
P16	49	Male	Right	Ischaemic	85	9.1%	Minimal

Table 2 | Adverse events.

	Rotigotine	Placebo
Fatigue	4* (25%)	1 (6%)
Topical skin reaction	1 (6%)	0
Nausea	5† (31%)	0
Vomiting	1 (6%)	0
Diarrhoea	2‡ (13%)	0

Number of patients with at least one occurrence. *7 events in 4 patients. †9 events in 5 patients. ‡3 events in 2 patients.

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