Exploring the use of dopaminergic medication to treat hemispatial inattention during in-patient post-stroke neurorehabilitation

Abstract

Hemispatial inattention (HSI), a lateralised impairment of spatial processing, is a common consequence of stroke. It is a poor prognostic indicator for functional recovery, and interferes with progress during in-patient neurorehabilitation. Dopaminergic medication has shown promise in improving HSI in the chronic post-stroke period, but is untested in more acute settings, eg during in-patient neurorehabilitation. We audited the use of dopaminergic medication in ten sequential patients with post-stroke HSI, on an open label exploratory basis. Patients' response to medication was assessed individually, using a three week Off-On-Off protocol. We employed a mixture of bedside and functional measures, and made a multi-disciplinary judgement of efficacy in individual patients. In six out of ten patients, there was convincing improvement of HSI while on medication, which reversed when it was paused. There was a mean 57% relative increase in target detection in the star cancellation test on the most affected side (on vs off medication). In the six responders, medication was therefore continued for the duration of their admission without adverse effects. The star cancellation test was sensitive to HSI in most patients, but in two cases failed to detect changes that were picked up by a functional assessment (Kessler Functional Neglect Assessment Protocol). We found this approach of multi-disciplinary assessment to be feasible in an in-patient

neurorehabilitation setting. We suggest further research to explore the efficacy of dopaminergic medication, with the aim of improving neurorehabilitation outcomes in patients with post-stroke HSI. We suggest that more detailed N-of-1 assessments of treatment response, with internal blinding, may be a productive approach.

Introduction

Stroke is the most common cause of adult disability worldwide. In the UK it affects >110,000 patients each year, with an overall associated annual cost of around £9 billion. Hemispatial inattention (HSI, or neglect) is the inability to respond equally to stimuli across space. It is most commonly caused by stroke (present in 50-82% of patients with acute stroke; Buxbaum et al 2004) and persists into the chronic phase in approximately a third of these (Karnath et al 2011). During the time in which patients with more significant neurodisability are receiving intensive rehabilitation HSI is therefore a frequent obstacle to making functional gains.

When assessed soon after stroke onset, increasing HSI predicts greater long term functional dependence independent of stroke severity (Luvizutto et al 2018), and in a recent UK study its presence at first assessment predicted a more than double length of hospital stay than if it were absent (Hammerbeck et al 2019). Persistent HSI is a stronger predictor of chronic dependence than hemiplegia or overall stroke severity (Oh-Park et al 2014), and when present in chronic stroke is correlated with poorer quality of life (Sobrinho et al 2018).

During in-patient neurorehabilitation HSI presents a significant obstacle to patients' ability to engage with therapy: treating therapists will typically struggle to

bring the patient's attention over to the affected side during functional task practice such as washing or dressing, resulting in limited progress during sessions and reduced functional independence once the rehabilitation programme is complete. Interventions which reduce HSI severity in this early phase may therefore enable greater functional gains from neurorehabilitation and reduce long term disability. Given the association of persistent HSI with poor functional outcomes, and the difficulties experienced by treating therapists in treating patients within the affected side of space, developing potential strategies to improve it must be a priority for neurorehabilitation research.

Existing therapeutic strategies

A range of strategies have attempted to improve HSI symptoms, many using practical measures to re-direct the patient's attention into the impaired half of space, intrapersonal or extrapersonal according to context. These include Limb Activation, Space remapping, Mental Imagery, Sustained Attention Training, Feedback Training, Vestibular Stimulation, Optokinetic Stimulation, Neck Muscle Vibration, eye patching and Music therapy (Luauté et al 2006). The evidence base for these strategies is not well established however, and most are not in wide clinical use. The mainstay rehabilitation approach for HSI to date has been visual scanning therapy, often in the form of Smooth Pursuit Training, in which visual targets are tracked into the neglected hemifield. This technique can improve behavioural measures of neglect in single sessions and as regular therapy (Hopfner et al 2015; Kerkhoff et al 2014). Non-invasive brain stimulation shows some promise as an adjunctive strategy, in most cases using cathodal transcranial direct current stimulation to down-regulate activity in the intact parietal lobe. This can be used either alone (Hopfner et al 2014) or in combination with other therapies (O'Shea et al 2017), but its wider application is

limited by technical availability, and there is little evidence that its effects generalise to functional gains (Brighina et al 2003; Lim et al 2003; Koch et al 2012; Koch et al 2008).

The technique of Prism Adaptation uses a set of customised glasses to induce a shift in visual stimuli away from the affected side of space. This induces a compensatory corrective shift in reaching movements towards the affected side which induces patients to attend to the neglected side. This effect generalises in some studies to multiple functional domains (see Jacquin-Courtois et al 2013 for review), and can persist for several months in some (Serino et al 2009; Mizuno et al 2011) but not all (Nys et al 2008; Turton et al 2010) studies. This approach may be helpful as an adjunctive treatment in some patients, but a recent meta-analysis of 7 eligible studies showed no overall benefit over placebo (Qiu et al 2021).

A number of centres have explored pharmacological approaches to alleviating HSI, focusing primarily on the cholinergic, dopaminergic and noradrenergic systems (Paolucci et al 2010; Mukand et al 2001; Dalmaijer et al 2018). Such studies often include low patient numbers, and many take the form of case series or cohort studies, such that it has been difficult to draw firm conclusions regarding the efficacy of this approach. The heterogeneity of study designs has also made comparison difficult, and a Cochrane systematic review in 2015 identified only 2 completed studies out of 25 assessed that met criteria for inclusion, concluding that the overall quality of evidence from randomised controlled trials was very low (Luvizutto et al 2015).

Components of hemispatial inattention

HSI is not a unitary syndrome. Anatomically it usually results from damage within the territory of the middle cerebral artery, and has been most closely associated with damage to the inferior parietal lobule, the temporoparietal junction and the superior temporal gyrus (Vallar 2001; Husain & Rorden 2003; Karnath et al 2011). Variation in findings as to the neuro-anatomical correlate of HSI may well reflect the heterogeneity of the clinical syndrome, but consistently involve the elements of the attentional network. This also include the white matter tracts which link them, and the persistence of HSI into the chronic phase has been linked to damage to the superior longitudinal fasciculus (Lunven et al 2015). HSI is more common following damage to the right hemisphere, most likely due to the role of the right hemisphere in attentional processes.

HSI, as part of the wide clinical syndrome of 'neglect', may include a range of phenomena which have in common an asymmetry of behaviour (Bisiach & Luzzatti 1978; Posner et al 1984; Bartolomeo & Chokron 2002; Husain & Rorden 2003; Coulthard, Parton, & Husain 2006). These include reduced movement of the limbs of the affected side (assuming that the motor pathways are intact, which is often not the case in the case of larger strokes) compared to the unaffected side, so-called motoric neglect (Heilman et al 1985). Other examples include sensory or visual extinction, where a stimulus on the affected side is detectable if presented alone but is no longer perceived if presented together with a stimulus on the other side of space. (Bender 1952). These differing lateralised phenomena have given rise to a variety of models of HSI which seek to explain them, including a directional motor model (difficulty initiating movements towards the affected side, Heilman et al 1985), a representational model (inability to respond because the area of space no longer has a brain representation, Karnath et al 1991) and a spatially lateralised attentional

gradient model (difficulty directing attention to the affected side, Smania et al 1998). The latter example allows for the commonly observed attentional gradient across space, as distinct from a central meridian as observed in hemianopia for example. It seems likely that the diversity of clinical phenomena encountered within the rubric of HSI may reflect the fact that several or all of these models hold true to some extent in explaining the lateralised phenomena observed.

Over recent years there has been an increased appreciation that non-lateralised impairments also play an important role in the clinical manifestation of HSI (Husain & Rorden 2003). Impairments of cognitive abilities such as non-lateralised selective attention (inferior parietal lobe, superior temporal gyrus, Husain et al 1997), sustained attention (right frontal lobe, Robertson et al 1997) and spatial working memory (right intraparietal sulcus and inferior frontal gyrus, Wojciulik et al 2001; Husain et al 2002; Malhotra et al 2005; Malhotra, Coulthard & Husain 2009) are often observed in patients with HSI due to stroke, depending on the anatomy of the brain injury. Difficulty with stimulus salience detection (temporo-parietal junction) may also play a role (Husain & Rorden 2003). Moreover, many of these non-lateralised cognitive impairments correlate in their extent with the severity of HSI observed (Robertson et al 1997). To give a practical example, when performing a star cancellation task patients with HSI will often return to areas which they have already been through (impaired spatial working memory), may struggle to ignore the distractor elements of the chart (impaired salience detection) and may find that their performance flags as the task progresses (impaired sustained attention). This has led to the idea that while HSI is fundamentally an asymmetrical impairment of spatial perception or behaviour, its effects on functional tasks may be greatly exacerbated by the non-lateralised impairments that often accompany it.

The rationale for treating HSI with dopaminergic medication

Recent interest in the possible use of dopaminergic medication to alleviate HSI is founded on increased understanding of how anterior networks support spatially directed attention. In the healthy brain, dopaminergic neuromodulation is known to support some of the non-lateralised cognitive functions whose impairment contribute to HSI, specifically working memory and sustained attention (Wojciulik et al 2001; Malhotra et al 2005; Malhotra, Coulthard & Husain 2009) via prefrontal dopamine receptors (Goldman-Rakic, Muly & Williams 2000). Dopaminergic stimulation improves spatial working memory in healthy, aged monkeys and in those with spatial working memory deficits (Castner, Williams & Goldman-Rakic 2000; Castner, Williams & Goldman-Rakic 2004). Likewise spatial working memory may be improved in healthy humans by dopamine agonist medication (Muller von Cramon & Pollmann 1998). Thus it may well be that dopaminergic medication can act to alleviate HSI by supporting these non-lateralised cognitive processes.

Clinical studies so far have provided some support for this strategy, but in very small patient numbers and usually in the chronic post-stroke period. In one small study four patients received carbidopa-levodopa for a week, with three showing an improvement in bedside and functional tests, but with no control intervention (Mukand et al 2001). In another small case series, four patients received subcutaneous apomorphine (a dopamine agonist) and demonstrated improvements in performance of a circle crossing and pointing / counting tasks (Geminiani et al 1998). Amantadine is an NMDA receptor blocker with a weak dopaminergic effect: investigators in a further study gave amantadine to four patients with chronic HSI in

an ABA design but found no consistent effect over several outcome measures (Buxbaum et al 2007). Fleet et al (1987) gave the dopamine agonist bromocriptine to two patients with post-stroke HSI (one acute, one chronic) in an ABA design with transient beneficial effects. However two other studies have by contrast demonstrated detrimental effects of bromocriptine on HSI, in one case reducing exploration of the affected side during a target search task (seven patients, Grujic et al 1998) and in another worsening line bisection (study with single patient, Barrett et al 1999). Overall, the small patient numbers and lack of controls in these studies preclude meaningful conclusions regarding the efficacy this strategy, and none were deemed eligible for inclusion in the meta-analysis performed by Luvizutto et al (2015).

Most recently a randomised placebo-controlled trial of the D1/D2 agonist rotigotine in 16 chronic stroke patients with neglect demonstrated a significant improvement in selective attention to the affected side (Gorgoraptis et al 2012). The feasibility of applying this approach in clinical practice during neurorehabilitation early after stroke is however untested. We describe here an audit of our experience to date with giving dopaminergic medication to ten sequential in-patients on our neurorehabilitation unit with significant post-stroke HSI, assessing their response on a personalised basis in individual patients. We hypothesised that, in patients who are amenable to dopaminergic modulation of their attentional networks, we may see amelioration of HSI after the medication is started which would then relapse once it is stopped.

Methods

Study design and patient selection for treatment

This was a XXX – see comment. All patients treated were in-patients on our Neurorehabilitation Unit at the National Hospital for Neurology & Neurosurgery. All had received acute stroke treatment elsewhere before being transferred to our unit for in-patient neurorehabilitation, and were participating in an intensive therapy programme. Patients received daily input from a physiotherapist, an occupational therapist, and a speech & language therapist (Monday to Friday, with a rest at weekends), working towards discharge goals which were set near the start of their admission. They received an average of 3 neuropsychology sessions per week. Additional sessions were delivered ad hoc by a rehabilitation assistant and a social worker. Bedside care was delivered by neurorehabilitation-trained registered nurses, aiming to incorporate therapeutic strategies into personal care.

The clinical approach to treating each patient's HSI was not protocolled but rather was dependent on the functional difficulties observed. In physiotherapy, repetitive practice and explicit cognitive strategies were used to improve attention to limbs on the affected side, for example during transfers from bed to chair. In occupational therapy, visual scanning techniques such as the lighthouse strategy were employed during functional activities, for example in washing or kitchen tasks. If necessary, joint sessions were arranged to allow for input from more than one treating therapist during a difficult task.

We considered a trial of medication if there was noted to be significant post-stroke HSI sufficient to interfere with the process of rehabilitation. We considered patients regardless of whether they had ischaemic stroke or intracerebral haemorrhage, and we did not exclude patients on the basis of stroke laterality. We

excluded patients if 1) they were medically unstable (eg with intercurrent infection); 2) if they had a concurrent extrapyramidal disorder; or 3) there were felt to be clinical contra-indications to dopaminergic medication, such as hallucinations, agitation, hypersexuality or impulsivity.

Assessment and treatment protocol

The protocol for assessment and treatment is shown in Figure 1. All patients are discussed regularly at our Multidisciplinary Team (MDT) meeting. If a patient was felt by the team to demonstrate HSI sufficient to interfere with their progress then a trial of medication was proposed. If the consensus was to proceed then they would be screened for contraindications as listed above. If the dopamine agonist rotigotine were under consideration then an Electrocardiogram would be performed to exclude cardiac conduction defects (recommended for rotigotine, but not for co-careldopa). Assessment proceeded over three consecutive weeks: week 1 off dopaminergic medication; week 2 on dopaminergic medication; and week 3 off dopaminergic medication. Other medications were continued unchanged. During each of the three assessment weeks patients' HSI was assessed using the Star Cancellation Chart test, performed twice per week (approximately Days 2 and 5), and the Kessler Foundation Neglect Assessment Protocol (KFNAP). An Off-On-Off assessment process was used in order to allow for an overall trend for HSI to improve with time after stroke. A patient was deemed to have responded to medication if they showed improvement when it was started (Week 2) which subsequently reversed when it was discontinued (Week 3).

For each patient the outcomes of the HSI assessments were reviewed at the weekly MDT meeting, and a consensus decision taken as to whether the patient had

shown a clinically significant response. If this were the case then the medication was re-started for the remainder of the neurorehabilitation admission (Week 4 onwards). When the time for discharge was approaching, a further assessment was made in these patients, with a trial of discontinuing medication for one week (using the same assessments). If the HSI re-emerged off medication then this was re-started for discharge, with a further review in the out-patient clinic – otherwise the medication was discontinued at that point.

At the start of the period covered in this audit we used the Star Cancellation Chart test only. It became apparent that in some patients the therapy team were observing changes in HSI which were not being captured by that measure, so from P5 onward we added the KFNAP in order to provide an assessment more relevant to functional tasks.

Dopaminergic medication

Patients were excluded from consideration of treatment if they were medically unwell or had a contraindication to dopaminergic medication. For the first three patients we used the dopamine agonist rotigotine, given as a transdermal patch at a dose of 4 mg / 24 hours. Patients receiving rotigotine had an ECG first to assess cardiac conduction. As nausea is a more frequent side-effect of that medication we subsequently switched to the dopamine precursor co-careldopa, given orally at a dose of 100/25 mg TDS. Two days prior to starting the dopaminergic medication (ie on day 6 of week 1 of the assessment period) patients were also started on the anti-emetic Cyclizine at a dose of 50 mg TDS, to prevent nausea which is sometimes associated with dopaminergic treatment. This was discontinued at the end of Week 2.

Hemispatial Inattention assessments

The Star Cancellation Chart test (Wilson, Cockburn & Halligan 1987) is a bedside psychometric measure of HSI, and was performed by a doctor or treating therapist. It forms one element of the more comprehensive Behavioural Inattention Test (Halligan, Cockburn, & Wilsom, 1991), which includes a variety of tasks including cancellation, figure copying and line bisection tasks. We were keen to use a single element as our bedside measure in order to limit the time and effort burden for our patient group, who are prone to fatigue with longer assessment. We chose this element as cancellation tasks are more sensitive to HSI than bisection tasks (Ferber & Karnath 2001). The patient was sat at a table with the standard chart directly in front of them, the chart's centre aligned with their midline. The chart contained a mixture of stars shapes (large and small) and distractor letters and words. The patient was given a pencil and asked to draw a circle around each of the small stars, of which there were 27 on each side of the centre, while ignoring other shapes and letters. They were not given a time limit, and were asked to continue until they had circled all of the targets. They were scored according to the percentage of targets on the affected side of space correctly circled.

The KFNAP (Azouvi et al 2006) is an ecological assessment of HSI within a range of functional tasks, and was scored by the patient's treating Occupational Therapist. The patient was observed in ten functional contexts covering both intra-personal and extra-personal spatial attention (limb awareness, personal belongings, dressing, grooming, gaze orientation, auditory attention, navigation, collisions, eating, and cleaning after meal). For each the presence of HSI was rated from 0 (none) to 3 (severe), and the total expressed as a percentage of the maximum possible score (from the domains assessed). The KFNAP involves observing a

number of functional activities: this was either done over the course of a single day or across two days, depending upon the patient's activities. The therapy and medical teams were not blinded to medication, which was given here on an open label basis.

Analyses

According to the Off-On-Off assessment protocol outlined above, we were able to designate patients individually as responders or non-responders to medication, with respect to the outcome measures used but also from an overall clinical perspective. In patients for whom more data was available we could also follow outcome scores longitudinally. At the group level we tested for an effect of medication on Star Cancellation test scores using a one-way ANOVA, examining the effect of 'ON' (week 2) versus 'OFF' drug (weeks 1 and 3). The percentage correct on the affected side was the dependent variable. 'ON_OFF' was entered as a fixed factor and 'patient' as a random factor. Modelling the data in this way compares ON and OFF periods within-subject and removes any linear effects of time. We examined changes in the KFNAP score with medication in one patient (P9) for whom the Star Cancellation test was insensitive to his clinically evident HSI (this patient was excluded from the group level ANOVA). For this patient we performed KFNAP multiple assessments across several weeks. We compared scores ON versus OFF medication using a permutation test. This is a distribution-free N-of-1 analysis based on multiple rearrangements of the raw scores. A computed statistic, representing the difference in the means between the two conditions (ON vs OFF), is compared with the value of that statistic for all other possible arrangements of the data obtained in that patient. The P-value is the proportion of arrangements leading to a value of the statistic as large as, or larger than, the value obtained from the actual data.

Results

Clinical characteristics

The patients' clinical details are shown in Table 1, where they are listed in chronological order. All had ischaemic stroke except for two (P6 and P7) who had suffered an intracerebral haemorrhage. All had a stroke within the right cerebral hemisphere, except for one (P9) in whom the stroke was on the left side. Their median age was 53, with a median initial NIHSS (NIH Stroke Scale, where available) of 18. All had received acute stroke treatment elsewhere before being transferred to our unit for in-patient neurorehabilitation, and were participating in an intensive therapy programme. Each had hemispatial inattention contralateral to their stroke, judged by the multidisciplinary team (MDT) to be significantly obstructing their progress.

In all patients, evidence of HSI was observed during therapy sessions and when attempting functional tasks. The clinical manifestations of HSI in each patient are given in Table 2, but we highlight here more detailed examples from three patients as being illustrative of the variety of functional domains involved. P3 was noted to need prompting to incorporate his left arm in kitchen tasks, and to straighten out his t-shirt after dressing himself. He had normal somatic sensation and proprioception on the affected side. P3 also exhibited the 'pusher syndrome', a term which describes active pushing away from the non-hemiparetic side in the sitting position, and which is thought to reflect a distortion of the patient's sense of their own midline, associated with but not caused by HSI (Karnath & Broetz 1983).

P5 was noted not to attend to his left side during showering and dressing, requiring repeated prompting to scan to the left. He managed to wash both sides of his body but spent less time on the left, and during drying failed to monitor for correct drying of his left side despite prompts. During grooming he brushed only the right side of his teeth, failed to dry the left side of his mouth, and combed only the right side of his hair. As a result of the repeated prompts and re-directions required, his morning routine would take over 75 minutes to complete. When undressing at the end of the day he would fail to remove clothing from his left side. While using an electric powered wheelchair, he would fail to notice obstacles to the left and would consequently hit the left side of the door frame, which precluded independent use of the chair. When preparing breakfast in the therapy kitchen he demonstrated an asymmetrical approach, banging into the worktop with his left side. During physiotherapy sessions working on assisted pivot transfers he was reluctant to put weight through his left leg, despite the absence of any pain, limiting the extent of progress made with transfers. Figure 2 (A&B) shows attempts by P5 to copy a pair of intersecting pentagons and a 3-dimensional cube, both demonstrating inattention of the left side.

P8 needed extensive prompting to orientate to the left side of his body during therapy sessions, and could not maintain focus on the left arm during sensory stimulation. He also exhibited pushing to the left when sitting on a plinth, and struggled to maintain his midline when sitting in a shower chair. He was unable to locate a flannel that was sitting on his left arm despite prompting. During electric wheelchair assessment he was unable to drive in a straight line. Figure 2 (C) shows P8's attempt at a star cancellation task, in which the small stars through which he failed to draw a line are ringed.

Response to dopaminergic medication

Of the ten patients treated with dopaminergic medication, the first three received rotigotine and the subsequent seven co-careldopa. This change was made because of the relatively high incidence of nausea arising from rotigotine. Medication was started a median of 119.5 days post-stroke (see Table1). One patient experienced transient drowsiness on rotigotine, and one had a brief hypotensive episode while taking co-careldopa. No other medication side-effects were reported.

In one patient (P9) the star cancellation scores were normal despite clinically evident HSI: he used a very effective search strategy, methodically working his way across the page, and detected 100% of targets on both the affected and unaffected sides. Of the remaining nine patients, six showed a clear improvement in scores on medication in week 2, which then reversed once it was withheld in week 3 (Figure 3A). Of these, one (P7) did not show a corresponding clinical improvement in a functional context and was thus deemed a clinical non-responder despite his scores. At the group level (nine patients, Figure 3B – excludes P9), there was a significant improvement in star cancellation scores on medication, which reversed when it was discontinued (effect of drug, 1-way ANOVA: $F(1, 8) = 15.50$, $p = 0.004$) with a mean ON value of 77% and OFF of 49%, a relative improvement of 57%.

From P5 onwards we began to use the KFNAP alongside the star cancellation test, as a potentially more informative test with respect to functional tasks. Due to the relatively heavy demands on therapists' time, assessments were not fully completed for P7 or P8. The scores with respect to dopaminergic medication are shown for four patients in Figure 4A. For three patients (P5, P6 and P9) these show a reversible reduction in HSI while on medication: this response was not observed in P10. The

responses for these four patients were therefore concordant with the multidisciplinary team's impressions of clinical response as shown in Table 1. For the patient in whom star cancellation was insensitive to his HSI (P9) we performed serial KFNAP scores (Figure 4B), which demonstrated a reversible improvement on medication which corresponded with clinical change (48.2% reduction in inattention score, permutation testing on vs off treatment Z=2.07, p=0.057).

In total therefore, six out of ten patients in this group showed a clinical improvement in HSI on dopaminergic medication, regardless of their outcome scores. In four of the five clinical responders whose HSI was sensitive to star cancellation testing, this measure was tested again later in the admission (this data was unavailable for one patient). At this point, a mean of 118 days after medication was started, the apparent beneficial effect appeared to be sustained, though this was not formally tested: mean % targets identified on the affected side at each time point in these patients were 56.0 (Off1) - 94.1 (On) - 55.1 (Off2) - 90.7 (Late) respectively. In each of the six responders a trial withdrawal was made towards the end of their admission, to assess whether the medication was still effective at that point. This was the case in four of the six treated patients, and these were discharged on medication (to be re-assessed as an out-patient).

Discussion

Of the ten patients whom we treated with dopaminergic medication, six appeared showed a clear clinical response which reversed when the medication was paused. At the group level we observed a significant improvement in star cancellation scores while on medication, which reversed once it was discontinued. In

one patient for whom that test was insensitive to his HSI we observed a reversible improvement in KFNAP scores whilst taking the medication.

We cannot conclude from this data that dopaminergic medication is effective in improving HSI across the stroke population as a whole, which would require larger patient numbers. We likewise cannot draw any conclusions regarding the relative efficacies of rotigotine and co-careldopa in this context with such small numbers. More importantly, in any open label use of medication one must consider the real possibility that either the patient or the therapists were influenced in their performance / assessment by their knowledge of the medication being used. It would therefore require a blinded randomised clinical trial to resolve the question of efficacy.

These results do however demonstrate the feasibility of using dopaminergic medication for this impairment in the setting of subacute post-stroke neurorehabilitation. Our patients tolerated the medication well, with little in the way of side-effects. We found that the assessment process could be integrated into the patients' rehabilitation timetables without difficulty, and that it could identify patients who are responsive to this medication

We observed that our patients with HSI frequently demonstrated additional cognitive or perceptual impairments, which will also likely contribute to their functional outcomes. This is perhaps not surprising given that HSI is most commonly observed in the context of ischaemia within the territory of the middle cerebral artery, home to many important cognitive functions. In our patient group for example P5 showed difficulty in sustaining attention, with significant distractibility during therapy tasks that was also a treatment obstacle. P8 showed evidence of apraxia during

object use, and incorrect sequencing of tasks, suggesting wider deficits across the fronto-parietal networks than those of visuospatial function alone. Most of our patients showed evidence of a dysexecutive syndrome to some extent. None of our patients therefore had ‘pure’ HSI, but rather a heterogeneous combination of impairments, and in our experience this is typical.

Assessing HSI during neurorehabilitation

The star cancellation test was used in all of our 10 patients, and it was sensitive to the clinically evident HSI in all but one patient (P9). This patient showed evidence of left inattention in almost all functional domains, scoring 23.75 out of a maximum of 30 in the KFNAP (overall moderate-severe), and yet did not miss a single left sided star in the cancellation task and so scored 100%. This dissociation is interesting, and one might speculate that this patient developed a highly effective search strategy which allowed him to explore the available space on the chart systematically despite his HSI.

Likewise in one other patient (P7), medication was associated with a dramatic improvement in star cancellation (which reversed on pausing the medication) but the judgement of the MDT was nonetheless that no clinically meaningful change had been observed. Unfortunately we do not have KFNAP scores for that patient, but it seems likely that while they were on medication the star cancellation test again failed to detect their significant HSI. These two examples perhaps demonstrate the limitations of a paper-and-pen tests in detecting functionally relevant impairments.

This suggests that while the star cancellation task is quick to perform and less labour intensive than functional tests, nonetheless it may not be that useful as a screening tool in this context. Our results would imply that in patients who are

suspected to demonstrate HSI a more ecological and functionally relevant test such as the KFNAP would be better placed to serve as a screening tool. We would also advocate that regardless of the test results it is good practice to discuss the patient's response to medication with the MDT, and then come to a consensus view. This is because changes in functional performance may be observed by some members of the team but not others, presenting the risk of meaningful change being missed if there is not wide consultation. We therefore suggest that the approach of including both a bedside test and a functional measure, and then reviewing both in MDT discussion, allows the team to judge overall response in a way that will be meaningful in a neurorehabilitation context.

Future directions

A randomised controlled trial (RCT) would be needed to resolve at a group level the question of whether dopaminergic medication is effective in treating HSI during in-patient post-stroke neurorehabilitation. However an RCT would not necessarily be the most informative next step. Given the heterogeneity of both stroke syndromes and of HSI it would likely require large patient numbers to detect a group effect. We believe that our results provide some support for taking a more targeted approach, where N-of-1 trials are used to inform clinical decision making with regard to medication response in individual patients. RCTs examine the effect of a putative intervention on a group as a whole, detecting a change in the average. This misses the heterogeneity of responses across the population, risking both type 1 and type 2 errors as a result, and potentially failing to detect meaningful effects in susceptible patients. This may be particularly true when assessing a multi-modal complex impairment such as HSI. A more robust implementation of an N-of-1 approach would require a double-blind crossover design within each individual patient, whereby the

active medication and placebo are given at different times, unknown to the patient and treating team: the patient thereby acts as their own control (Husain 2021). This elegant approach has been used successfully in patients with chronic HSI (Gorgoraptis et al 2012), though not in the subacute stage. It requires a relatively large number of assessments in each patient, potentially more than may be feasible in an in-patient neurorehabilitation setting. Nonetheless, given the detrimental effect of HSI on engagement in neurorehabilitation, and thus on recovery from stroke, we argue that such an approach would be worth exploring in more detail. Assessments of this kind, embedded within a neurorehabilitation programme and monitored by a multi-disciplinary team, have the potential to improve the robustness of clinical decisions in this context.

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Patient	Age	Stroke type	Region	R / L handed	Medi-cation	Days post	FIM-FAM	Star canc baseline	Star canc response	KFNAP response	Clinical response
P1	51	ISCH	R MCA	LH	ROT	19	82	50	Y	-	Y
P2	55	ISCH	R MCA	RH	ROT	110	150	38	Y	-	Y
P3	60	ISCH	R MCA	RH	ROT	127	67	72	Y	-	Y
P4	51	ISCH	R ACA/MCA	RH	CO-C	120	110	45	N	-	N
P5	50	ISCH	R MCA	RH	CO-C	75	103	64	Y	Y	Y
P6	68	HAEM	R tempo-parietal	RH	CO-C	172	56	0	Y	Y	Y
P7	47	HAEM	R basal ganglia	RH	CO-C	119	107	15	Y	-	N
P8	69	ISCH	R MCA	RH	CO-C	125	93	93	N	N	N
P9	60	ISCH	L MCA	RH	CO-C	123	89	100	-	Y	Y
P10	51	ISCH	R MCA	RH	CO-C	50	87	17	N	N	N

Table 1.

Clinical features of the ten patients included here. All had clinically significant post-stroke hemispatial inattention, and were assessed during an in-patient stay on a Level 1 Neurorehabilitation Unit. Days post-stroke is the day on which dopaminergic medication was first started. The FIM-FAM scale (Functional Independence Measure - Functional Assessment Measure, maximum score 210) is a measure of functional independence across a range of motor and cognitive domains. The score shown is that on admission for neurorehabilitation. A star cancellation response is not given for P9, as this measure was

insensitive to hemispatial inattention in that patient, who made no errors on that test despite clinically evident HSI. ACA = Anterior Cerebral Artery; MCA = Middle Cerebral Artery.

Patient	Clinical manifestation of hemispatial inattention
P1	Missed left side when performing personal care and washing. Required written prompts to perform scanning to the left side initially. Poor safety awareness to the left side, particularly when outside and trying to cross a road.
P2	Needed verbal prompts to attend to her left side when locating objects in the shower room, or on the bathroom sink. Also required frequent prompts to scan to the left during kitchen tasks, eg to take the toast out of the toaster.
P3	Was unable to maintain his midline while sitting, pushing with overactive R side. Needed prompting to incorporate left arm during kitchen task. Needed prompting to straighten t-shirt after dressing.
P4	Poor acceptance of weight onto the left side and overactivity of the right during sliding board transfers and during therapeutic standing. Needed prompts to attend to left side during washing. Asymmetrical donning of shirt during dressing, with left side crumpled. Making pizza, he bunched the toppings to the right side of the pizza base.
P5	Did not attend to left side during personal care, showering and dressing. Combed only right side of head. Required extensive prompting to left, so morning routine taking > 75 minutes. Failed to remove clothing from L arm during undressing. Unsafe to use electric power chair, as ignoring obstacles to left side and hitting left side of door frame.
P6	Poor midline orientation when lying in bed, left leg hanging off the bed's edge. Had difficulty standing with weight on the left leg despite good power. Reduced attention paid to the left side during washing face or brushing teeth, brushing hair or applying face cream.
P7	In kitchen tasks, chopped vegetables only on the right side, only seasoned chicken to the right, and spread onto one half of toast. Asymmetrical midline during standing despite visual feedback, lack of awareness of left leg position. Unsafe use of powered wheelchair due to making contact with objects on the left side.
P8	Needed prompting to orientate to left side of body, particularly L hand. Pushed to left with overactive right side while sitting. Needed verbal prompts to attend to left side when washing himself. Did not see or feel a flannel sitting on his left arm. Unable to drive electric wheelchair in a straight line.
P9	Needed verbal prompts to scan for items to the right in the supermarket. Did not attended to a saucepan with potatoes on the right hand side during cooking. When undressing, only removed gown from left arm and only removed his left sock. After shower only dried left side of body when given a towel. Brushed left side of teeth only.
P10	Gaze preference to the right, not attending to left arm when in wheelchair. Difficulty reading starts of sentences. Only searched the right hand side of a drawer when looking for clothes. Did not notice toothpaste spilt onto the left hand. Impaired midline awareness during transfers. Failure to locate the oil to the left during a cooking task.

Table 2.

Examples of hemispatial inattention in our patient group, as manifested while attempting functional tasks.

Figure 1

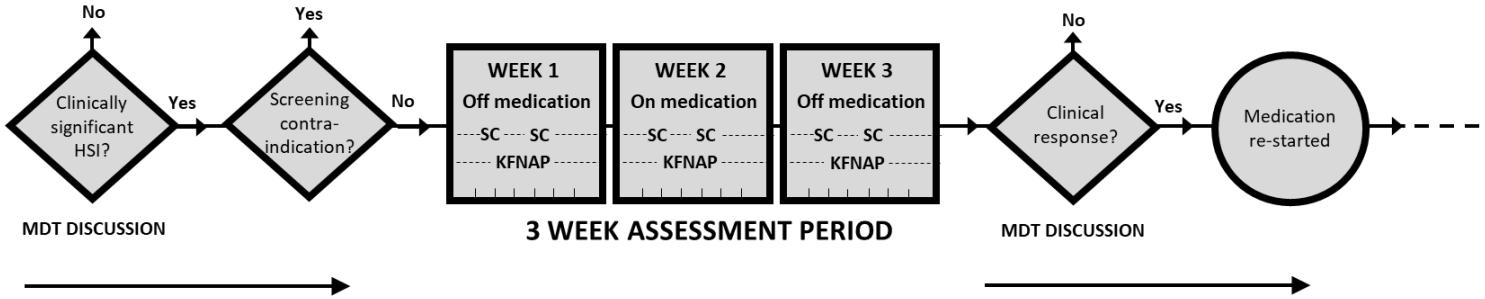


Figure 1.

The assessment protocol we used to determine whether an individual patient responds to dopaminergic medication. After identifying potentially suitable patients and screening for contraindications, patients were assessed over a 3 week period as shown (OFF-ON-OFF), with tests of Hemispatial Inattention in each week. The decision as to whether a clinical response was observed was taken at a multi-disciplinary team discussion.

Figure 2

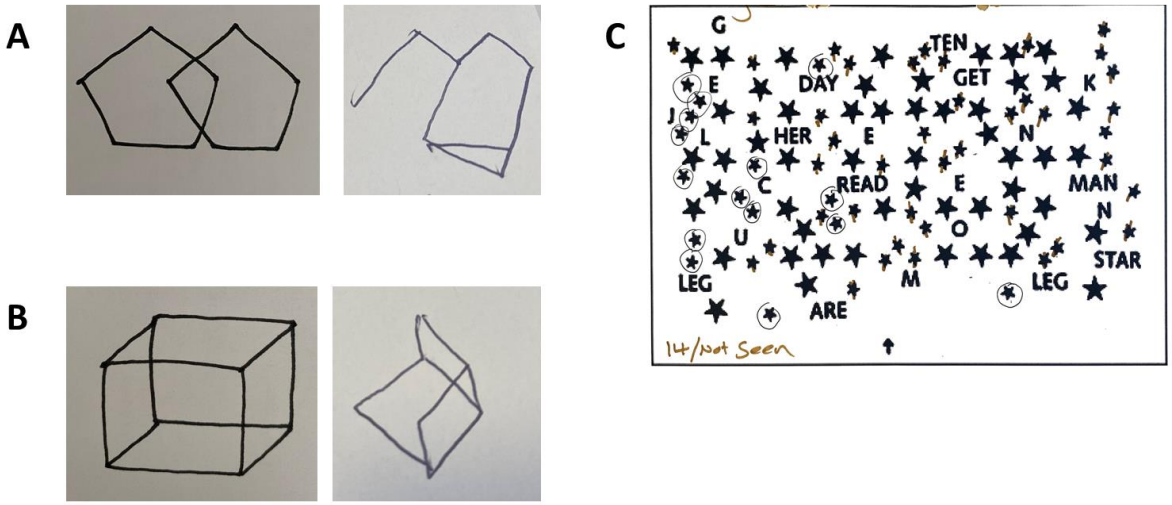


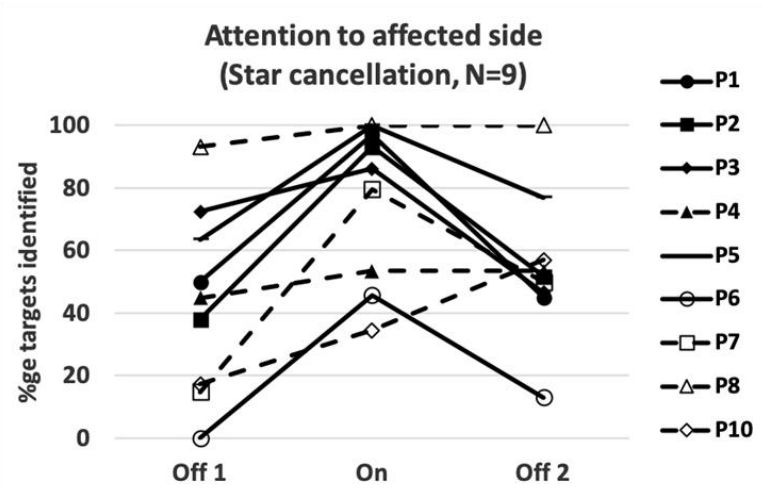
Figure 2. Examples of Hemispatial Inattention in our patients

A. Attempts by patient P5 to copy a pair of intersecting pentagons and a 3-dimensional cube, both demonstrating inattention of the left side.

B. Patient P8's attempt to complete a star cancellation task. The instruction was to put s line through every small star, ignoring large stars and other distractors. No time limit was set. The ringed stars show those that were missed, in this case 14 on the left-most part of the chart, indicating significant hemispatial inattention of the left side.

Figure 3

A


Attention to affected side
(Star cancellation, N=9)
%ge targets identified
100
80
60
40
20
0
Off 1
On
Off 2
P1
P2
P3
P4
P5
P6
P7
P8
P10

B

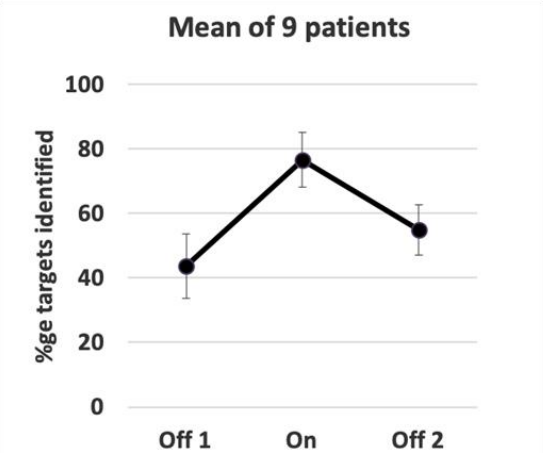
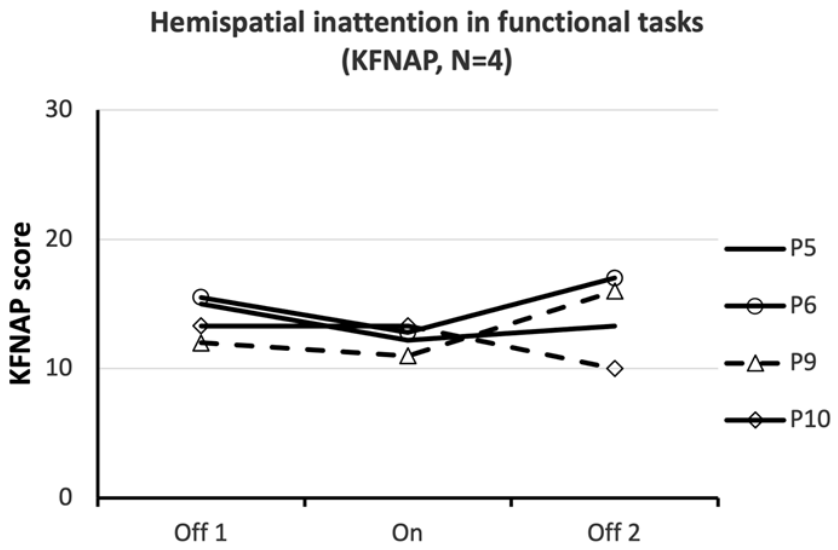

Mean of 9 patients
%ge targets identified
100
80
60
40
20
0
Off 1
On
Off 2

Figure 3. Effect of dopaminergic medication on star cancellation scores

A. Star cancellation scores are shown for individual patients across the three week ‘ABA’ design assessment period. Scores are given for the week before medication (Off1), on medication (On) and the week after it was discontinued (Off2). Data is shown for nine of the ten patients: in P9 this test was insensitive to his clinical HSI.
B. The mean star cancellation scores are shown across the assessment period (for the group of nine patients in whom the test was sensitive to their hemispatial inattention). There was a significant improvement on medication (see text), with an effect size of 57% (on vs off medication).

Figure 4

A


Hemispatial inattention in functional tasks
(KFNAP, N=4)
KFNAP score
30
20
10
0
Off 1
On
Off 2
P5
P6
P9
P10

B

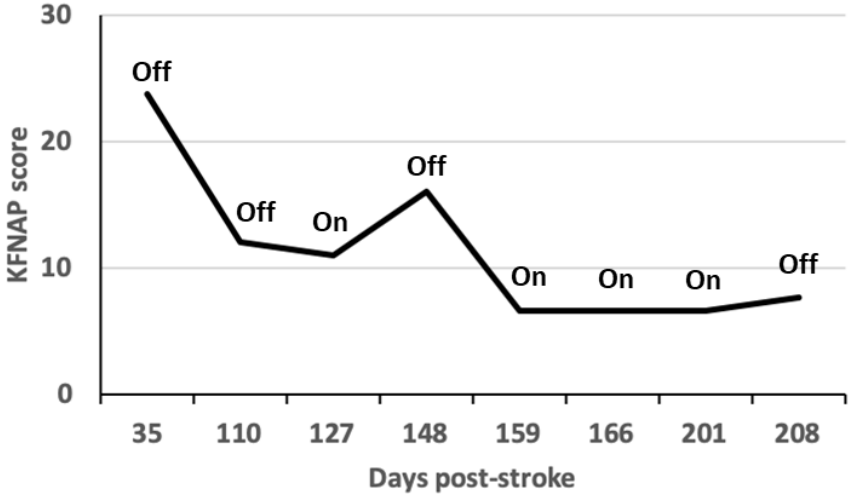

KFNAP score
30
20
10
0
Off
Off
On
Off
On
On
On
Off
35
110
127
148
159
166
201
208
Days post-stroke

Figure 4. Kessler Foundation Neglect Assessment Protocol (KFNAP) scores

A. KFNAP scores with respect to dopaminergic treatment for four patients. P5, P6 and P9 showed reversible improvements while on medication, while P10 did not, in keeping with the overall clinical impression of the multidisciplinary team for these patients.

B. Serial KFNAP scores for P9, who showed marked clinical HSI but normal scores on the star cancellation test. Here we show the KFNAP scores (a measure of HSI observed in functional tasks) for this patient in relation to the use of dopaminergic medication, with day post-stroke of the assessment shown on the x-axis. He was deemed a clinical responder. A natural history of improvement is seen, but discontinuing the medication was associated with a relapse of clinical HSI.