

Available online at www.sciencedirect.com



Brain and Cognition 55 (2004) 497-506



www.elsevier.com/locate/b&c

# Subcortical modulation of spatial attention including evidence that the Sprague effect extends to man

Rodger A Weddell\*

Neurosciences Directorate, Morriston Hospital, Swansea Wales, UK Department of Psychology, University of Wales, Swansea Wales SA2 8PP, UK

> Accepted 24 February 2004 Available online 13 April 2004

## Abstract

The Sprague effect is well-established-small tectal lesions restore visual orientation in the hemianopic field of animals with extensive unilateral geniculo-striate lesions. Studies of human midbrain visual functions are rare. This man with a midbrain tumour developed left-neglect through subsequent right frontal damage. Bilateral orientation returned after clear evidence of damage to the superior colliculus contralateral to the cortical lesion (showing the Sprague effect extends to man). Sustained right-neglect developed after probable additional damage to right superior colliculus. The regulation of spatial attention by tecto-pulvinar circuits is discussed, and it is argued that the reduced right tecto-pulvinar activity (consequent to the additional right collicular damage) was offset by over-compensatory increase in thalamic reticular nucleus (TRN) suppression of left pulvinar activity. © 2004 Elsevier Inc. All rights reserved.

Keywords: Superior colliculus; Visual neglect; Recovery

## 1. Introduction

Cats with unilateral striate plus dorsal and ventral stream extrastriate cortical damage do not orient to contralateral visual stimuli. Remarkably, Sprague (1966) restored orientation by ablating (a) the contralesional (on the side opposite the cortical lesion) superior colliculus or (b) the intertectal commissure. Several laboratories have replicated this effect (Sprague, 1996).

Recent work on cortical contributions to spatial attention shows that cooling confined to the feline homologue of parietal cortex produces neglect, which is remediated by cooling the opposite (a) superior colliculus or (b) parietal cortex (Lomber & Payne, 1996). It further suggests cooling of feline anterior cortex might produce neglect reversible with parietal or collicular cooling on the opposite side (Lomber & Payne, 2001). Indeed, right parietal neglect resolved after a left frontal lesion in one patient (Vuilleumier, Hester, Assal, & Regli, 1996): the authors implicated competitive cortical-subcortical modulations of spatial attention, involving the superior colliculi and/or the thalamic nucleus reticularis (TRN).

Research on midbrain contributions demonstrates contralateral neglect after unilateral damage to the superior colliculus (Sprague, 1996; Stein & Meredith, 1993), the mesencephalic reticular formation (Watson, Heilman, Miller, & King, 1974), and the substantia nigra pars compacta (Schultz, 1982). Moreover, studies of the Sprague effect show that attention is modulated by competitive interactions between left and right midbrain circuits. Thus, cooling one superior colliculus induces contralateral neglect: bilateral orientation is restored when the opposite colliculus is concurrently cooled (Lomber & Payne, 1996). Moreover, orientation returns in a visual field rendered hemianopic through unilateral visual cortical ablation when the ipsilesional superior colliculus is disinhibited with a GABA antagonist (Ciaramitaro, Todd, & Rosenquist, 1997). Apparently, the ipsilesional superior colliculus is inhibited by projections from critical contralesional zones in (a) the substantia

<sup>&</sup>lt;sup>\*</sup> Fax: +44-1792-703455.

*E-mail addresses:* r.weddell@virgin.net, linda.young@swansea-tr. wales.nhs.uk.

nigra pars reticulata and (b) a mesopontine reticular formation structure, the pedunculopontine tegmental nucleus. This is because ablation of the latter midbrain sites and/or their projections via the intertectal commissure also restores orientation (Durmer & Rosenquist, 2001; Wallace, Rosenquist, & Sprague, 1989, 1990).

There are occasional studies of the effects of human midbrain damage on covert spatial attention. Studies of Parkinson's disease usually record no deficit, but patients with progressive nuclear palsy were slow in moving covert visual attention in the vertical plane (Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988). It is particularly difficult to obtain human evidence of the Sprague effect. Large brainstem lesions are often associated with a high mortality rate, marked motor deficits, and/or considerable cerebral hemispheric damage: unsurprisingly, the visual effects of superior colliculus damage appear to have been studied in only one human case (Zihl & vCramon, 1979). Additionally, the superior colliculus must be damaged in a patient with pre-existing neglect from cerebral hemispheric damage. Nevertheless, this report describes perhaps the first human case of the Sprague effect. AD, who had a midbrain tumour, exhibited left unilateral neglect after acquiring right frontal damage incurred in the management of an episode of hydrocephalus. Neglect disappeared seven months later, after a transient visual disturbance, which indicated additional superior collicular damage, as regular brain scans yielded no evidence of additional cor-

Table 1

Summary of main clinical and neuroradiological developments in study phases

tical damage. A second transient visual disturbance 17 months later was followed by sustained mild right-sided neglect, suggesting that additional superior collicular damage altered the left–right balance again.

## 2. Methods

#### 2.1. Case report

In May 1994, AD, a 34-year-old right-handed man, developed hydrocephalus (Table 1) through aqueduct obstruction by a grade 3/4 glioma verified by MRI guided biopsy. Dr. E.W. Jones, Consultant Neuroradiologist, who was blind to hypotheses under test, reviewed brain scans and located lesion site using an atlas of the cerebral hemispheres (Mai, Assheuer, & Paxinos, 1997) and of the brain stem (Paxinos & Huang, 1995). MRI on 9.27.94 confirmed normalisation of ventricular size by a right parietal shunt, and only two cuts showed tumour (Table 1). It infiltrated the dorsal mesopontine midline surface (Fig. 1A, showing superior colliculus). The cut above (Fig. 1B, showing intertectal commissure, Com) reveals an apparently normal layer suggesting relative preservation of the surface layers of the superior colliculi (which modulate visual spatial attention (Lomber & Payne, 1996)), the lateral superior colliculi, and the lateral left subadjacent tegmentum. The entire ventral midbrain also appeared normal. A course of radiotherapy followed.

	Period	Clinical developments	Radiological developments	
Diagnosis and initial treatment	5.23.94-6.30.94	Right parietal shunt inserted CT(6.30.94): Normal ventricles		
Post-diagnosis (PD)	10.7.94-8.23.95	Recovery-no longer employed but fairly active	very-no longer MR (9.27.94): Tumour in midbrain (Figs. 1A and B); oyed but fairly active normal ventricles; normal cerebral hemispheres	
Coma	10.5.1995–10.31.95	Right parietal shunt blocked, right frontal drain inserted (10.5.95); left parietal shunt inserted (10.18.95)	ight parietal shunt locked, right frontal drain iserted (10.5.95); left arietal shunt inserted 0.18.95) CT (5.10.95–11.9.95): Hydrocephalus-temporarily resolved by frontal drain $\rightarrow$ recurred $\rightarrow$ permanently resolved by left parietal shunt	
Post-coma (PC)	PC <sub>b</sub> : 12.20.95–5.15.96	Left neglect in PC <sub>b</sub>	CT (5.1.96): New right frontal hypodensity in $PC_b$ ; slight generalised atrophy; no other cerebral hemispheric anomaly; normal ventricular size	
	PC <sub>a</sub> : 5.29.96–11.29.97	PC <sub>a</sub> starts with right visual field disturbance, restoring bilateral orientation; return to more active life	CT (9.13.96): No new hemispheric lesions (CT and MR found no subsequent cortical change in $PC_a$ through $R$ )	
Quiescence 1 (Q1)	Q1 <sub>b</sub> : 3.12.97–10.29.97	Fairly active life (e.g., gardening)	—	
	Q1 <sub>a</sub> : 11.19.97–3.24.98	$Ql_a$ starts with left-lower scotoma; right neglect from $Ql_a$ to R	MR (9.26.97): Structural changes in midbrain appearances including surface collicular invasion & small cyst under right superior colliculus	
Quiescence 2 (Q2)	4.28.98-5.10.99	Fairly active	CT (9.23.98): Small expansion of midbrain cyst	
Recurrence ( <i>R</i> )	6.9.99–5.17.00	Gradually increasing forgetfulness, tiredness, diplopia, and motor rigidity	MR (9.26.99, see Figs. 1C and D). Substantial cyst growth right medial thalamic damage, but no cortical change. No change in MR on 4.19.00 or CT on 7.18.00	



Fig. 1. MRI horizontal sections showing lower (A and C) and upper (B and D) midbrain. Top: post-diagnosis (PD, 27.9.94); arrows indicate the left superior colliculus (SC) in 2A and the textal commissure (Com) in 1B. Bottom: recurrence (*R*, 30.9.99).

Shunt failure in October 1995 induced coma. Hydrocephalus was relieved, temporarily via a right frontal ventricular drain, then permanently via a left parietal shunt. Hydrocephalus never recurred. On emerging from coma, AD exhibited left-sided neglect and CT on 5.1.96 demonstrated a new dorsolateral frontal hypodensity in three cuts along the track of the now-removed right frontal drain and Table 1 shows that subsequent scans showed no cortical damage additional to the right frontal anomaly and slight generalised cerebral atrophy. AD became quite active after recovery from coma in 1995. Initial vertical diplopia resolved in February 1996. Visual acuity was poorest (J16, right; J12, left) in December 1995, improving to J4 in both eyes 9 months later.

He reported two transient visual disturbances affecting both eyes (having closed each in turn). First, AD described two episodes of distorted right peripheral vision (in May and June 1996) as being like "... looking through rain on a window". Each lasted for two days, and occurred without headache. Importantly, Table 1 shows that CT on 9.13.96 found no evidence of left hemisphere damage (though it and all subsequent scans confirmed the right frontal lesion evident via CT on 5.1.96). Second, he observed a transient left lower quadrantic scotoma in November 1997. He saw a distinct "... zigzag L-shaped line..."; he saw objects above the line but not those immediately below it (Fig. 2); this lasted for half a day and was not associated with headache. MR at this point (9.26.97) indicated that the midbrain anomaly was essentially the same size as it was on 9.27.94, but its internal structure had changed. For example, there was a new 0.7 cm cyst under the lateral right superior colliculus, which represents the left lower quadrant (Stein & Meredith, 1993), and the abnormality now extended right through the dorsal wall of the superior colliculus. This left field scotoma was not associated with radiological evidence of new right cerebral hemispheric damage (Table 1). These deficits presumably signify new focal damage to the retinotopically organised superior colliculus (Stein & Meredith, 1993) for two reasons. First, both field defects occurred when lesion evolution was evidently confined to the midbrain, there being no evidence of additional cerebral hemispheric damage from 5.1.96 to 5.17.00. Second, collicular lesions produce transient contralateral field deficits



Fig. 2. AD's drawing of the left lower field scotoma.

in monkeys (Albano, Mishkin, Westbrook, & Wurtz, 1982).

CT on 9.23.98 showed slight cyst growth. Perimetry on 11.14.98 showed full fields for detection of visual stimuli. By 9.26.99, MRI found the cyst virtually replacing the dorsal midbrain and tegmentum, and infiltrating the ventral and left lateral midbrain (Figs. 1C and D). Two cuts are not shown: the tumour tip extended one cut up on the right, probably just into the medial pulvinar and posterior hypothalamus, and clearly into the ventromedial wall of the thalamic dorsomedial nucleus. Left thalamus appeared spared, but tumour conceivably extended into the medial wall of the dorsomedial nucleus and medial pulvinar. A 1-cut downward extension invaded the right inferior colliculus, and dorsal tegmentum. Growing forgetfulness began in summer 1999. This and subsequent stiffness and ataxia in all limbs increased gradually until 5.17.00, though he could always walk and use his hands, and he continued to distinguish bilateral and unilateral light touch and sound. Vertical diplopia returned in late 1999, mixed with horizontal diplopia. Visual acuity was J6– J10 on the left, and J6–J12 on the right between December 1999, and May 2000. Perimetry on 2.28.00 found full fields for detection of visual stimuli. MR in 4.19.00 did not indicate significant tumour growth.

#### 2.2. Neuropsychological testing

Test data were pooled across the following mostly 1year periods, which were also tied to clinical stages: Post-diagnosis (PD, from 10.7.94 to 8.23.95), Post-coma (PC, 12.20.95–1.29.97), relative Quiescence 1 (Q1, 3.12.97–3.24.98), Quiescence 2 (Q2, 4.28.98–5.10.99), and Recurrence (R, 6.9.99–5.17.00). The PC stage was further subdivided into the phases before ( $PC_{before} \rightarrow PC_b$ ), and after ( $PC_{after} \rightarrow PC_a$ ) transient right peripheral visual impairment. Similarly, Quiescent 1 was subdivided into phases before (Q1<sub>b</sub>), and after (Q1<sub>a</sub>) the left lower field scotoma. Table 1 links phases with clinical and neuroradiological developments.

Standardised assessments, (performed in PD, PC<sub>a</sub>, and the start and end of *R*), yielded relatively normal scores (Spreen & Strauss, 1998). Thus, from 1994 to May 2000, Verbal Fluency (FAS) was consistently low average. Low Wechsler Memory Scale Logical Memory and Visual Reproduction scores remained within normal limits, while Paired Associate learning remained impaired. Recognition memory for faces was consistently poor. WAIS–*R* Full Scale IQ (PD=101 to R = 106) was comparable to the National Adult Reading Test premorbid IQ-estimate (Range=95–100).

#### 2.2.1. Number search test

Ninety 2-digit  $3 \times 3$  cm numbers were randomly distributed on  $42 \times 30$  cm sheets, producing six different 15number arrays. Twelve larger 90 cm wide arrays were constructed using three sheets. One array was placed on a desk, AD and experimenter facing each other across its vertical meridian. Using a pseudorandom schedule, AD searched for 12 aurally presented numbers: 3 from the leftsided, central, and right-sided sheets, and 3 numbers were absent (being on other sheets). A stopwatch measured latencies of AD's first response. Only immediate selfcorrections were accepted-the recorded latency for self-corrected responses being time to judge the number absent. Self-corrections were rare as AD systematically searched arrays left-to-right and did not re-scan the array after the first pass. Up to four different arrays were used per test occasion. Viewing was monocular, and order of eye use was counterbalanced. Minimising errors was AD's first priority with speed second. Data were gathered in notional "sessions" of four consecutive arrays. "Sessions" were mostly monthly. They were performed in a single test occasion between 10.4.94 and 4.1.96, and over two occasions thereafter.

Four uninjured control subjects with acuities across the range exhibited by AD also performed four 12-trial blocks in 6 separate test sessions: C1 (46 years; both J2), C2 (60; right J12, left, J14), C3 (62; both J14), and C4 (54; right J10, left J12).

#### 3. Results

#### 3.1. Errors

Each eye yielded the same results, permitting pooling of these data. A loglinear model evaluated the effects of



Fig. 3. AD's visual search misses by side and period.

Period (PD vs. PC<sub>b</sub> vs. PC<sub>a</sub> vs. Q1<sub>b</sub> vs. Q1<sub>a</sub> vs. Q2 vs. *R*), Side (Left vs. Right), and Height (Above vs. Below Midline) on Errors (Hit vs. Miss). The significant Period × Side × Error interaction was the critical result (change in  $\chi^2_{df=6} = 38.32$ , p < .001). This partly reflected a small linear growth in total misses over the years (Mantel–Haenszel  $\chi^2_1 = 9.66$ , p < 0.002). It also reflected 3 shifts in predominant error laterality (Fig. 3). Thus, right and left-sided errors were equally frequent during PD. The first shift appeared on recovery from coma in the PC<sub>b</sub> phase, when he missed only one right target. This significant left-neglect ended abruptly in a second shift, which followed the right peripheral visual disturbance (see Section 2.1).

In the third shift, right-neglect followed the transient left field scotoma (see Section 2.1) marking the start of the  $Q1_a$  phase: it continued through Q2 and R.

Predominant error laterality was consistent within phases. Excluding the two 48-trial sessions where the proportion of left- and right-sided errors was equal, the proportion of sessions producing more right-sided errors varied with phase as follows: PD (60%), PC<sub>b</sub> (0%), PC<sub>a</sub> and Q1<sub>b</sub> (46.2%), Q1<sub>a</sub> (3 of 4 = 75%), and for the 25 months of Q2-*R* (100%).

## 3.2. Latencies

Trial order (r = .00, NS) and number of misses (r = -0.03, NS) in 12-trial blocks did not influence correct search latency. Correct latencies were the dependent variable in a  $7 \times 3 \times 2$  ANOVA. Total search time was included by pseudorandomly coding number absent (NA) trials as above or below the midline. Side (NA vs. Left vs. Right), Period, and Height were factors.



Fig. 4. Mean search times for right- and left-sided hits and number absent trials by period.

Side  $(F_{2,2451} = 1371.44, p < .001)$ , Height  $(F_{1,2451} =$ 6.70, p < .01), and Side × Height ( $F_{2,2451} = 10.07$ , p < .001) were significant because AD almost invariably searched in a left to right direction (Fig. 4) starting from the upper left quadrant and finishing in the right lower or upper quadrant. Period ( $F_{6,2451} = 117.44, p < .001$ ), and Period × Side ( $F_{12,2451} = 9.91$ , p < .001) were significant. Table 2 shows that this was because NA, righttarget, and left-target latencies were longer than baseline during PC<sub>b</sub> (when right frontal damage and left-neglect appeared). Moreover, latencies fell towards baseline levels during PC<sub>a</sub> (after the right-sided visual disturbance) but NA and right-target trials remained selectively longer than baseline. Finally, NA latencies were longer than baseline after the left-sided scotoma during Q1<sub>a</sub>. No other term was significant.

If AD's subjective experience during NA responses were the same on miss and NA trials, we might expect

Table 2 Mean (*SD*) of correct latencies for controls and for AD by phase (\* marks difference from  $PD_{-p} < .05$ )

matrix difference from $PD^{-}p <, p$						
	Number	Left		Right		
absent		Lower	Upper	Lower	Upper	
AD						
PD	8.9 (2.0)	4.4 (1.9)	3.7 (2.6)	7.2 (2.1)	7.0 (2.3)	
$PC_b$	13.1 (2.3)*	5.9 (2.7)*	4.8 (3.2)*	10.3 (2.7)*	10.0 (3.7)*	
$PC_a$	10.8 (1.6)*	4.5 (1.5)	3.2 (1.7)	8.5 (2.2)*	8.1 (2.3)*	
Q1 <sub>b</sub>	8.9 (1.5)	3.9 (1.4)	3.3 (1.7)	7.1 (1.7)	7.0 (1.6)	
Q1 <sub>a</sub>	9.7 (1.6)*	4.3 (1.5)	4.0 (2.6)	7.2 (1.7)	7.5 (2.2)	
Q2	8.6 (1.6)	3.9 (1.9)	3.1 (1.7)	7.1 (1.6)	7.0 (1.4)	
R	8.6 (1.8)	3.9 (1.5)	3.3 (1.9)	6.9 (1.9)	7.3 (2.2)	
Controls						
C1	8.2 (1.4)	3.6 (1.5)	2.7 (1.3)	6.1 (1.8)	5.8 (1.8)	
C2	13.4 (2.4)	10.6 (2.6)	3.8 (2.4)	10.2 (3.1)	4.8 (1.8)	
C3	8.4 (1.5)	3.8 (1.7)	2.8 (1.4)	3.9 (1.4)	5.4 (1.4)	
C4	6.9 (1.3)	4.4 (1.7)	3.4 (1.8)	3.2 (1.2)	3.3 (1.5)	

miss and correct NA responses would have the same latencies. To test this, miss, and NA latencies were divided by the mean latency of the 3 NA trials in each 12trial block. By definition, this latency ratio yields a mean value of 1.0 for NA trials. Clearly, mean miss ratios significantly greater than 1 indicate that AD took longer to report a number's absence when it was actually there than when it was actually absent. In other words, though miss and NA trials elicited identical verbal responses, significant elevation of miss latency ratios suggests covert awareness of the missed number. Most importantly in the present context, miss ratios of 1, and above suggest that AD searched the array as thoroughly as usual on that trial. Conversely, ratios significantly below 1 indicate that all or part of the array may have been scanned cursorily. It should be noted that a constant miss ratio across periods implies a constant speed-accuracy trade-off. A  $5 \times 3$  ANO-COVA evaluated the effects of Period (PD vs. PC vs. Q1 vs. Q2 vs. R) and Side (Left vs. Right vs. NA) on latency ratios (pooling phases and heights yielded at least 5 cases per cell). Lastly, AD occasionally expressed concern when he had missed a few items. Growing uncertainty may have prolonged latencies of later trials in those blocks eliciting more than 3 NA responses; consequently, Trial Order, the number of misses, and their multiple (to evaluate their interaction) were covariates.

Side was significant ( $F_{2,791} = 6.76$ , p < .001), left and right miss ratios being similarly greater than 1 from PC to *R*; i.e., across *all* shifts in predominant error laterality (Table 3 and Fig. 5). Period was not significant ( $F_{4,791} =$ 0.54, NS). Period × Side ( $F_{8,791} = 2.81$ , p < .004) was significant because, during PD, right-sided miss ratios were below NA ratios while left-sided ratios were particularly high. Trial Order was significant ( $F_{1,791} = 10.13$ , p < .002) because ratios tended to decrease during trial blocks, perhaps due to increasing familiarity of the array. The Miss ( $F_{1,791} = 0.60$ , NS) and the Miss × Trial Order ( $F_{1,791} = 0.26$ , NS) interaction covariates were

Table 3 Mean (SD) of miss latency ratios for AD by phase and for Controls

	Left	Right			
AD					
PD	1.20 (0.2)	0.80 (0.2)			
PC	1.06 (0.2)	1.07 (0.1)			
Q1	1.07 (0.2)	1.04 (0.2)			
Q2	1.06 (0.3)	1.08 (0.2)			
R	1.07 (0.2)	1.09 (0.2)			
Controls (Left and Right)					
C1	1.03 (0.2)				
C2	1.02 (0.1)				
C3	1.02 (0.1)				
C4	0.97 (0.1)				



Fig. 5. Mean miss ratios for right- and left-sided misses and number absent trials by period.

insignificant: importantly, latency ratios did not increase monotonically with the number of misses.

# 3.3. Control data

Unlike AD, controls equally often missed right and left targets ( $\chi^2$  range = 0.7–1.95, NS). AD made as many errors as C1–C3 (5.6–7.4%;  $\chi_3^2$  = 2.07, NS), but fewer than C4 (12.5%;  $\chi_1^2$  = 5.02, p < .03).

Table 2 includes latency data for each control subject. Subject, Side (Left vs. Right vs. NA), and Height (Above vs. Below Midline) were factors in a  $5 \times 3 \times 2$ ANOVA with correct latencies as the dependent variable. Subject was significant ( $F_{4,3546} = 188.52, p < .001$ ), latencies being ordered as follows: C4 (M = 4.5 s, SD = 2.2 s < C1 (M = 5.6, SD = 2.5) & C3 (M = 5.5, SD = 2.5)SD = 2.6 < AD (M = 7.3, SD = 3.4) < C2 (M = 9.0,SD = 4.4). Side ( $F_{2,3546} = 629.95$ , p < .001), Height  $(F_{1,3546} = 96.33, p < .001),$  Height × Side  $(F_{2,3546} =$ 27.50, p < .001), Subject × Side ( $F_{8,3546} = 39.75$ , p < .001) .001), Subject × Height ( $F_{4,3546} = 38.20$ , p < .001), and Subject × Height × Side ( $F_{8,3546} = 11.30$ , p < .001) were significant because search patterns varied. Thus, AD and C1–C3 searched systematically, C2 scanned top to bottom from upper left to left or right lower corners, the rest searching left to right from the left upper corner. C4 searched least systematically, beginning on the left, centre, or right.

Table 3 includes control miss latency ratios. C1–C3 who, like AD, searched systematically obtained miss latency ratios that were non-significantly above unity. C4 ratios were non-significantly below 1. Thus, AD searched for longer but made fewer errors than C4, who searched least systematically, fitting her eventual comment that speed was her first priority: AD's miss ratios

were higher than hers (t = 3.41, p < .001), confirming his greater emphasis on accuracy.

#### 4. Discussion

This study shows that AD developed left-sided neglect in PC<sub>b</sub> after incurring right frontal damage in the management of the hydrocephalus and coma ending PD. The abrupt disappearance of neglect 7 months later is attributed to the Sprague effect, since it coincided with the transient appearance of a right peripheral visual disturbance, which indicated lesion extension into the left superior colliculus (subsequent scans, CT 3 months and MR 15 months later, indicating lesion development in brainstem but not cortex). Seventeen months after reporting the right field defect, AD observed a transient left quadrantic scotoma consistent with neuroradiological changes in the right superior colliculus, and subsequently developed right-sided neglect lasting for 25 months (Q1<sub>a</sub>–*R*).

Lateralised shifts in speed-accuracy trade-off might explain these results. For example, more rapid and cursory leftward scanning might explain left-neglect during PC<sub>b</sub>, while the later right-neglect may reflect over-compensatory left-sided scanning following further right-brain attentional dysfunction (Robertson et al., 1994). However, AD applied the same left-to-right search strategy throughout the study. More importantly, hit latency ratio (hit latency ÷ mean NA latency per 12-trial block) measured the proportion of total search time to find each target, and that proportion was not lower for left-sided hits when he neglected the left in  $PC_b$  (M = 0.40) than when neglect resolved in  $PC_a$ (M = 0.35). Moreover, left-sided miss latency ratios remained above unity in PC<sub>b</sub> and PC<sub>a</sub>. Similarly, the right-neglect in  $Q1_a$ -R correlated with average left-sided and right-sided hit latency ratios, and average aboveunity miss ratios. More generally, after PD, left- and right-sided hit and miss latency ratios did not deviate significantly from the average despite clear shifts in the side neglected.

Changing relative salience of left- and/or right-sided numbers can explain these shifts. It is assumed that leftand right-sided objects are retinotopically represented in their respective contralateral cerebral hemisphere (Gaffan & Hornak, 1997), and spatial attention depends on establishing a complex balance in competing reciprocally connected cortical–subcortical circuits. Cortically, reciprocally connected parietal, prefrontal, and cingulate cortices regulate spatial attention in primates (Heilman, Valenstein, & Watson, 2000). Subcortically, single cell recordings suggest that the superior colliculus also modulates visual attention (Desimone, Wessinger, Thomas, & Schneider, 1990; Kustov & Robinson, 1996), these ascending influences paralleling its descending regulation of overt eye and body spatial orientation through its pontine, medullar, and spinal projections (Stein & Meredith, 1993). Indeed, already reviewed studies of the Sprague effect show that interactions between the superior colliculus, substantia nigra, and midbrain reticular nuclei maintain the right-left balance of spatial attention. Fig. 6 shows that the midbrain influence on cortical activity is partly exerted through dense projections from the superficial layers of the superior colliculus to the pulvinar (Robinson & Cowie, 1997), which is reciprocally connected with parietal, prefrontal, and cingulate cortical regions mediating spatial attention (Romanski, Giguere, Bates, & Goldman-Rakic, 1997). Moreover, in the monkey, single cell studies reveal medial pulvinar involvement in covert spatial attention and unilateral pulvinar deactivation also induces neglect (Robinson & Cowie, 1997), while pulvinar lesions induce neglect in man (Karnath, Himmelbach, & Rorden, 2002). Another thalamic structure, the reticular nucleus (TRN), has also been accorded a central controlling attentional/intentional role (Heilman, Watson, & Valenstein, 1993).

The TRN wraps the dorsal thalamus, receives collateral input from the "vertical" posterior and anterior thalamocortical and corticothalamic axons that must pass through it. The TRN solely outputs descending inhibitory projections to most dorsal thalamic nuclei (Fig. 6). Its blanket-like gating of sensory input to the cortex during sleep demonstrates a global function (Steriade, Jones, & McCormick, 1997). However, its inhibitory contributions are also local (Steriade et al., 1997). Indeed, Guillery, Feig, and Lozsadi (1998) review evidence of often precise topographical organisation within visual and other TRN sectors, which each have precise topographic relationships with thalamic nuclei and cortical regions. Also considering the convergence of information from several cortical areas on particular



Fig. 6. Superior colliculus projects to pulvinar, which reciprocally connects with frontal and parietal cortices. Thalamocortical and corticothalamic collaterals from several circuits converge on TRN cells, which mediate lateral inhibition in the pulvinar.

TRN sectors, Guillery et al. (1998) suggest TRN's strategic position might permit "... a highlighting of limited parts of thalamo-reticular circuits and can be closely related to Crick's 'searchlight hypothesis' about TRN action in attention." In other words, the inhibitory influence of the TRN on thalamic nuclei might mediate competition between different cortical-subcortical circuits "carrying" different sensory-motor representations. With specific regard to spatial attention, Fig. 6 represents the visual sector of the TRN. It shows that cell groups in pulvinar and cortex are reciprocally connected through ascending and descending projections, each sending collaterals to a TRN cell. The precise connectivity of the TRN has not been determined, but at least one layer of the visual sector is retinotopically organised (Guillery et al., 1998), and it is likely that reciprocally connected cortical and pulvinar cell groups representing a particular spatial location send axon collaterals to the same TRN population (Fig. 6). Moreover, Pinault and Deschenes (1998) found that TRN cells usually inhibited thalamic cells that did not project to them (Fig. 6). They argued that the latter feature coupled with mutually inhibitory interactions between the TRN cells themselves (Fig. 6) indicate that the TRN mediates lateral inhibition. Thus, competitive inhibitory TRN modulations of pulvinar activity might allow one spatially located object representation to suppress (i.e., to reduce salience of) several rival competing spatially located object representations. Indeed, unilateral neurotoxic lesions (destroying cell bodies and sparing fibres of passage) of the TRN covering the rodent homologue of the pulvinar impair covert spatial orientation on the contralateral side (Weese, Phillips, & Brown, 1999).

According to the foregoing model, the frontal lesion appearing at the start of  $PC_b$  reduced net right cortical– subcortical activation by left-sided objects, thereby potentiating left-brain suppression of right-brain attentional activity partly through left midbrain inhibition of the right superior colliculus. The subsequent right visual field disturbance starting  $PC_a$  indicated lesion extension into the left superior colliculus. This presumably reduced left midbrain inhibition of right tectal activity, and abruptly ended left-sided neglect.

The subsequent left-field scotoma very probably indicated further right superior collicular damage, since MRI at that stage demonstrated structural change confined to the midbrain. However, since MRI 2 years after appearance of the left-field defect indicated probable tumour invasion of the right medial pulvinar, conceivably, the first stages of tumour extension into the right pulvinar caused the left-field defect. In any event, the suggested additional damage to right tecto-pulvinar circuits was expected to induce left-neglect but, in fact, a 25-month phase of right-neglect followed. It might be argued that the left-field scotoma was associated with a degree of bilateral tumour infiltration into the pulvinar, which was greater in left medial pulvinar (thereby producing rightsided neglect). However, scans subsequent to the left-field defect strongly suggest greater tumour development in right thalamus, left cerebral hemisphere cortical and subcortical structures appearing relatively intact from PD to R. Of course, right-brain lesions sometimes induce right-sided neglect (Robertson et al., 1994); consequently, it is argued that the left-field scotoma signalled further compromise of tecto-pulvinar activity, which reduced midbrain activation of the right (but not the left) cerebrum. This deactivation necessitated the resetting of the balance of activity between left and right attentional circuits. Importantly, the resetting of cerebral hemispheric subcortical-cortical attentional circuits alone was probably sufficient, since right neglect was evident throughout *R*, when the superior colliculus was destroyed bilaterally (Fig. 1D). Several mechanisms of enhancing leftward attention are conceivable, since several interacting hemispheric cortical-subcortical mechanisms maintain the left-right attentional balance. However, bearing in mind the TRN's global gating of sensory inflow during sleep (Steriade et al., 1997), it is argued that the net effect of these mechanisms was to globally enhance left TRN inhibition of the left pulvinar. It is further suggested that the hypothesised increase in left TRN inhibition was overdone (causing right-neglect from  $Q1_a$  to R), perhaps through loss of the midbrain balancing mechanisms (underlying the Sprague effect).

The following implications warrant consideration. First, the Sprague effect is robust in cats and rats (Sprague, 1996). It parallels evidence that orientation is restored in neglect patients by vestibular stimulation of the contralesional ear (Rode et al., 2002) and by damage to the opposite cerebral hemisphere (Vuilleumier et al., 1996), while left neglect was eliminated after damage to the left superior colliculus in this study. Therefore, stereotactic lesions of the tectal commissure or the contralesional superior colliculus may restore visual orientation in patients with neglect and, intriguingly, one feline study found that sectioning the intertectal commissure restored a visual function other than spatial orientation (Sprague, 1991). However, to the author's knowledge, the present study provides the first indication that the Sprague effect extends to human and nonhuman primates. Clearly, further exploration of this effect in non-human primates is essential before seriously considering surgical intervention in man.

Second, there is evidence that covert awareness of complex visual forms in patients lacking primary visual cortex depends on visual input from the superior colliculus. For example, GY successfully discriminated words in his blind field (Marcel, 1998), while fMRI demonstrated differential superior collicular responses to emotional facial expressions presented in his hemianopic field (Morris, DeGelder, Weiskrantz, & Dolan, 2002). However, Fendrich, Wessinger, and Gazzaniga (1992) point out that studies have failed to exclude the possibility that blindsight reflects the residual visual capacity of functioning cortical islands. In the present study, search times were longer for missed numbers than for absent numbers. AD's significantly greater than unity miss ratios indicate significant covert awareness of the missed number forms. Interestingly, miss ratios remained above unity despite bilateral destruction of the superior colliculi throughout R, indicating that the cerebral hemispheres mediated covert awareness of number forms (at least in the present study).

#### Acknowledgments

I was fortunate to collaborate with AD, who lived positively and generously, even when facing the tumour, its discomforts, and his demise. His family's support was essential, especially the kind help of Chris, Raymond, and Rose, who regularly and reliably brought him to hospital. E.W. Jones, Consultant Neuroradiologist, very kindly reviewed the scans, and I appreciate useful discussion of relevant medical issues with J.L. Martin, R.M. Redfern, Consultant Neurosurgeons. The author thanks the anonymous reviewers' for their most helpful suggestions.

## References

- Albano, J. E., Mishkin, M., Westbrook, L. E., & Wurtz, R. H. (1982). Visuomotor deficits following ablation of monkey superior colliculus. *Journal of Neurophysiology*, 48, 338–351.
- Ciaramitaro, V. M., Todd, W. E., & Rosenquist, A. C. (1997). Disinhibition of the superior colliculus restores orienting to visual stimuli in the hemianopic field of the cat. *Journal of Comparative Neurology*, 387, 568–587.
- Desimone, R., Wessinger, M., Thomas, L., & Schneider, W. (1990). Attentional control of visual perception: Cortical and subcortical mechanisms. *Cold Spring Harbour Symposium Quantitative Biol*ogy, 55, 963–971.
- Durmer, J. S., & Rosenquist, A. C. (2001). Ibotenic acid lesions in the pedunculopontine region result in recovery of visual orienting in the hemianopic cat. *Neuroscience*, 106, 765–781.
- Fendrich, R., Wessinger, M., & Gazzaniga, M. S. (1992). Residual vision in a scotoma: Implications for blindsight. *Science*, 258, 1489–1491.
- Gaffan, D., & Hornak, J. (1997). Visual neglect in the monkey: Representation and disconnection. *Brain*, 120, 1647–1657.
- Guillery, R. W., Feig, S. L., & Lozsadi, D. A. (1998). Paying attention to the thalamic reticular nucleus. *Trends in Neurosciences*, 21, 28– 32.
- Heilman, K. M., Valenstein, E., & Watson, R. T. (2000). Neglect and related disorders. *Seminars in Neurology*, 20, 463–470.
- Heilman, K. M., Watson, R. T., & Valenstein, E. (1993). Neglect and related disorders. In K. M. Heilman & E. Valenstein (Eds.), *Clinical Neuropsychology* (third ed., pp. 279–336). New York: Oxford University Press.
- Karnath, H., Himmelbach, M., & Rorden, C. (2002). The subcortical anatomy of human spatial neglect: Putamen, caudate nucleus and pulvinar. *Brain*, 125, 350–360.

- Kustov, A. A., & Robinson, D. L. (1996). Shared neural control of attentional shifts and eye movements. *Nature*, 384, 74–77.
- Lomber, S. G., & Payne, B. R. (2001). Task-specific reversal of visual hemineglect following bilateral reversible deactivation of posterior parietal cortex: A comparison with deactivation of the superior colliculus. *Visual Neuroscience*, 18, 487–499.
- Lomber, S. G., & Payne, B. R. (1996). Removal of two halves restores the whole: Reversal of visual hemineglect during bilateral cortical or collicular inactivation in the cat. *Visual Neuroscience*, 13, 1143– 1156.
- Mai, J. K., Assheuer, J., & Paxinos, G. (1997). Atlas of the Human Brain. San Diego: Academic Press.
- Marcel, A. J. (1998). Blindsight and shape perception: Deficit of visual consciousness or of visual function. *Brain*, 121, 1565–1588.
- Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2002). Differential extrageniculostriate and amygdale responses to presentation of emotional faces in a cortically blind field. *Brain*, 125, 350–360.
- Paxinos, G., & Huang, X. (1995). Atlas of the Human Brainstem. San Diego: Academic Press.
- Pinault, D., & Deschenes, M. (1998). Anatomical evidence for a mechanism of lateral inhibition in the rat thalamus. *European Journal of Neuroscience*, 10, 3462–3469.
- Rafal, R. D., Posner, M. I., Friedman, J. H., Inhoff, A. W., & Bernstein, E. (1988). Orienting of visual attention in progressive supranuclear palsy. *Brain*, 111, 267–280.
- Robinson, D. L., & Cowie, R. J. (1997). The primate pulvinar: structural, functional, and behavioural components of visual salience. In M. Steriade, E. G. Jones, & D. A. McCormick (Eds.), *Thalamus, Volume 2: Experimental and Clinical Aspects* (pp. 53–92). Oxford: Elsevier.
- Robertson, I. H., Halligan, P. W., Bergego, C., Homberg, V., Plizzamiglio, L., Weber, E., & Wilson, B. A. (1994). Right neglect following right hemisphere damage. *Cortex*, 30, 199–213.
- Rode, G., Tilikete, C., Luaute, J., Rossetti, Y., Vighetto, A., & Boisson, D. (2002). Bilateral vestibular stimulation does not improve visual hemineglect. *Neuropsychologia*, 40, 1104–1106.
- Romanski, L. M., Giguere, M., Bates, J. F., & Goldman-Rakic, P. S. (1997). Topographic organization of medial pulvinar connections with the prefrontal cortex in the rhesus monkey. *Journal of Comparative Neurology*, 379, 313–332.
- Schultz, W. (1982). Depletion of dopamine in the striatum as an experimental model of Parkinsonism: Direct effects and adaptive mechanisms. *Progress in Neurobiology*, 18, 121–166.
- Sprague, J. M. (1991). The role of superior colliculus in facilitating visual attention and form perception. *Proceedings of the National Academy of Science*, 88, 1286–1290.
- Sprague, J. M. (1966). Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat. *Science*, 153, 1544–1547.
- Sprague, J. M. (1996). Neural mechanisms of visual orienting responses. *Progress in Brain Research*, 112, 1–15.
- Spreen, O., & Strauss, E. (1998). A Compendium of Neuropsychological Tests (second ed.). New York: Oxford University Press.
- Stein, B. E., & Meredith, M. A. (1993). Merging of the Senses. Cambridge, MA: MIT Press.
- Steriade, M., Jones, E. G., & McCormick, D. A. (1997). Thalamus, Volume 1: Organisation and Function. Oxford: Elsevier.
- Vuilleumier, P., Hester, D., Assal, G., & Regli, F. (1996). Unilateral spatial neglect recovery after sequential strokes. *Neurology*, 19, 184–189.
- Wallace, S. F., Rosenquist, A. C., & Sprague, J. M. (1990). Ibotenic acid lesions of the lateral substantia restore visual orientation behavior in the hemianopic cat. *Journal of Comparative Neurology*, 296, 222–252.
- Wallace, S. F., Rosenquist, A. C., & Sprague, J. M. (1989). Recovery from cortical blindness mediated by destruction of nontectotectal

fibres in the commissure of the superior colliculus in the cat. Journal of Comparative Neurology, 284, 429–450.

- Watson, R. T., Heilman, K. M., Miller, B. D., & King, F. A. (1974). Neglect after mesencephalic reticular formation lesions. *Neurology*, 24, 294–298.
- Weese, G. D., Phillips, J. M., & Brown, V. J. (1999). Attentional orienting is impaired by unilateral lesions of the thalamic reticular nucleus. *Journal of Neuroscience*, 19, 10135–10139.
- Zihl, J., & vCramon, D. (1979). Collicular function in human vision. *Experimental Brain Research*, 35, 419–424.