Published in final edited form as:
Behav Neurosci. 2009 February ; 123(1): 125–136. doi:10.1037/a0013734.

ROLE OF A LATERALIZED PARIETAL-BASAL GANGLIA CIRCUIT IN HIERARCHICAL PATTERN PERCEPTION:

EVIDENCE FROM PARKINSON'S DISEASE

Haline E. Schendan, Ph.D.[1,3], **Melissa M. Amick, Ph.D**[1,2], and **Alice Cronin-Golomb, Ph.D.**[1]

1*Department of Psychology, Boston University, 648 Beacon St., 2nd floor, Boston MA 02215, USA*

2*Department of Medical Rehabilitation, Memorial Hospital of Rhode Island, 111 Brewster Street, Pawtucket, RI 02860, USA*

3*Department of Psychology, Tufts University, The Psychology Building, 490 Boston Ave., Medford, MA 02155, USA*

Abstract

The role of corticostriatal circuits in hierarchical pattern perception was examined in Parkinson's disease. The hypothesis was tested that patients with right-side onset of motor symptoms (RPD, left hemisphere dysfunction) would be impaired at local level processing because the left posterior temporoparietal junction (TP) emphasizes processing of local information. By contrast, left-side onset patients (LPD; right hemisphere dysfunction) would show impaired global processing because right TP emphasizes global processing. Participants identified targets at local or global levels without and with attention biased toward those levels. Despite normal attentional control between levels, LPD patients showed a single dissociation, demonstrating abnormal global level processing under all conditions, whereas RPD patients showed abnormal local level processing mainly when attention was biased toward the local level. These findings link side of motor symptom onset to visuospatial cognitive abilities that depend upon the contralateral TP, highlighting that side of onset can predict visuospatial impairments, and provide evidence that an inferior parietal - basal ganglia pathway involving the caudate head and the hemispherically asymmetrical TP region is necessary for hierarchical pattern perception.

Keywords

hemispheric asymmetry; basal ganglia; neuropsychology; parietal lobe; visual spatial; Parkinson's disease

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Visuospatial problems are experienced regularly by patients with Parkinson's disease (PD), including difficulties during such diverse tasks as mental rotation, route walking, line bisection, perceptual closure, angle size estimation, and left-right decisions (reviewed in Cronin-Golomb & Amick, 2001). The extent, nature, and source of visuospatial impairment remain unclear, in part because some studies have not confirmed the existence of such deficits (Brown & Marsden,

Corresponding author: Haline E. Schendan, Ph.D., Department of Psychology, Tufts University, The Psychology Building, 490 Boston Ave., Medford, MA 02155, Telephone: 617-627-2143, Fax: 617-627-3181, Email: Haline_E.Schendan@tufts.edu.

1986; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Girotti et al., 1988). The discrepant findings may be explained to some extent by inattention to the potentially critical factor of body side of motor symptom onset. In our research, we have explored the hypothesis that PD patients with motor onset on the left side of the body (LPD) show visuospatial impairments reflecting their greater right hemisphere dysfunction, whereas PD patients whose onset was on the right side of the body (RPD) show visuospatial problems reflecting their greater left hemisphere dysfunction. We have obtained evidence suggesting a double dissociation between LPD and RPD groups on the well-established visuospatial task of mental rotation when left versus right visual field presentation was used, respectively (Amick, Schendan, & Cronin-Golomb, 2006). In this study, we aimed to test the hypothesis that visuospatial problems in PD reflect dysfunction in a lateralized corticostriatal network involving dorsal posterior cortical areas. We investigated the relation between side of onset and hierarchical pattern perception (HPP) and attention. These cognitive abilities have been shown to depend primarily upon lateralized areas in parietal cortices implicated in visuospatial transformation and attention but not the dorsolateral prefrontal cortex (DLPFC) to which visuospatial deficits in PD are often attributed.

In an HPP task, participants view hierarchically arranged stimuli (e.g., large letters composed of small letters) and identify targets occurring at the global (large) or local (small) level (Navon, 1977). In healthy adults, a right visual field (left hemisphere) advantage results when detecting local targets in a hierarchical pattern and a left visual field (right hemisphere) advantage occurs when global targets are detected (Sergent, 1982). Neuroimaging studies have revealed greater right posterior temporal-parietal junction (r-TP) activation during global processing and greater left TP (l-TP) activation during local processing, and the pattern of findings suggest TP may mediate the sustained distribution of attention between and across global and local visuospatial levels by modulating image analysis in more ventral extrastriate regions (Fink et al., 1996; Fink et al., 1997a,b).

Most relevant, studies of patients with damage in r-TP and l-TP suggest these areas are critical for global and local processing, respectively. Patients with r-TP lesions (intact left hemisphere) demonstrate a reaction time (RT) advantage when target stimuli occur at the local level relative to the global level, whereas patients with l-TP lesions (intact right hemisphere) manifest a RT advantage for target stimuli presented at the global relative to the local level. These findings indicate that the r-TP has an advantage for processing information at the global level, whereas the l-TP has a specialized role for processing information at the local level, though both hemispheres contribute to some extent to both global and local analysis (Lamb, Robertson & Knight, 1989; Robertson, Lamb, & Knight, 1988).

Performance on HPP tasks can also reveal impaired control of visuospatial attention. The ability to attend strategically to different hierarchical levels is disrupted after damage to the left rostral inferior parietal lobule (l-IPL) (Robertson et al., 1988). In studies with healthy adults that manipulate the probability of the level where the target occurs, a RT advantage is demonstrated when targets appear at the more probable (attention-biased) level relative to less probable level (Robertson & Lamb, 1991). Patients with r-TP or l-TP lesions benefit, as do normal individuals, from this probability information. By contrast, patients with l-IPL lesions fail to demonstrate a RT cost when the target appears at the less probable level (Robertson et al., 1988). While, to our knowledge, this type of visuospatial attention has not been examined in patients with rIPL lesions, a neuroimaging study with normal participants has shown activation in both left and right inferior parietal cortex when attention is biased toward one level or the other (Wilkinson, Halligan, Marshall, Buchel, & Dolan, 2001).

Unlike other visuospatial tasks, the particular HPP and attention tasks chosen for the present study have been demonstrated in prior neuropsychological work not to depend upon the

DLPFC. Whereas TP and IPL patients are impaired at HPP and attention, patients with damage in right or left DLPFC show no impairment (Robertson et al., 1991). If PD patients are impaired on the tasks herein, this would provide key evidence that problems with visuospatial cognition in PD can reflect dysfunction in parietostriatal connectivity, as opposed to a DLPFC-striatal loop involved in executive control to which PD visuospatial problems are usually attributed (e.g., Bondi, Kaszniak, Bayles, & Vance, 1991). If so, then the PD results would constitute evidence for the novel hypothesis that a parieto-basal ganglia pathway is necessary for HPP and attention.

Body side of motor symptom onset is important to consider when evaluating spatial cognition in PD because the right hemisphere, and particularly the right posterior parietal lobe, is necessary for processing spatial information (reviewed in Cronin-Golomb & Amick, 2001; Ogden, 1990). In PD, a unilateral onset of motor symptoms is typical. The asymmetrical motor symptoms observed in these patients have been associated with asymmetrical depletion of dopamine (DA) in the substantia nigra (SN) (Kempster, Gibb, Stern, & Lees, 1989) across the range of disease severity, from never-medicated patients with unilateral symptoms to medicated patients with more severe bilateral involvement (Antonini et al., 1995; Innis et al., 1993; Laulumaa et al., 1993; Leenders et al., 1990; Tissingh et al., 1998). The SN changes result in asymmetrical dysregulation of the striatum, which may lead to further asymmetrical dysfunction of multiple circuits involving the basal ganglia and cortical regions important for visuospatial abilities (Middleton & Strick, 2000a,b). Asymmetrical DA loss likely has consequences for the function of areas that receive inputs from or project to the basal ganglia, including the right posterior parietal regions important for visuospatial cognition (Clower, Dum, & Strick, 2005).

LPD patients with greater loss of DA in the right basal ganglia may be at higher risk for some spatial deficits than those with RPD with greater DA loss in the left basal ganglia. On a line bisection task, Lee and colleagues (2001a) found that LPD patients demonstrated mild left hemispatial neglect (bisected the line to the right of the true midline), whereas RPD and healthy control participants demonstrated a mild leftward bias. In another study, Lee and colleagues (2001b) asked individuals with PD to judge if they could fit through a virtual doorway. The LPD group overestimated the amount of space they would require to fit through the doorway, while the RPD group showed normal to mild underestimation.

Consistent with an asymmetry of basal ganglia dysfunction, we have demonstrated opposite visuospatial impairments in LPD and RPD patients in the same experiment using a visuospatial task of mental rotation (Amick et al., 2006). This task was selected because convergent findings indicate it depends upon the parietal cortex. Findings revealed a double dissociation for the LPD and RPD groups between mental rotation tasks with hand stimuli differing in visual-field presentation. These results suggested that the hemifield location of a to-be-rotated hand stimulus can cause frontoparietal networks in the left versus right hemisphere to be differentially engaged. Moreover, frontostriatal motor systems and the parietal lobes play a necessary role during the mental rotation of hands, which requires integrating visuospatial cognition with motor imagery. For the present work, we predicted we would also obtain opposite visuospatial impairments in LPD and RPD patients on the HPP and attention tasks.

These studies highlight that LPD and RPD patients may show different and even opposite patterns of visuospatial impairments. Consequently, in studies that do not consider side of motor symptom onset, the deficits may cancel each other out, and results would fail to accurately describe the spatial abilities of PD patients.

We propose that either an indirect or a direct pathway between the basal ganglia and parietal lobe is likely to underlie visuospatial problems in PD. An indirect route may involve the

DLPFC, which forms a large neural circuit with posterior parietal areas specialized for spatially-guided behavior (Selemon & Goldman-Rakic, 1988), and areas around the intraparietal sulcus send input primarily into the head of the caudate nucleus (Yeterian & Pandya, 1993), which is depleted of DA even at the earliest stages of PD (Kish, Shannak, & Hornykiewicz, 1988). Alternatively, evidence has been accumulating for a possible direct posterior parietal - striatal circuit; besides the projections to the caudate head, a posterior parietal region implicated in visuospatial cognition also receives output projections (via the thalamus) from the SN pars reticulata (SNpr) (Clower et al., 2005; Middleton & Strick, 2000a,b; Yeterian & Pandya, 1993). Given that the HPP and attention tasks herein have implicated posterior parietal areas but not DLPFC, a finding of opposite visuospatial impairments in LPD and RPD would favor a direct rather than indirect parietal-basal ganglia route.

The present study aimed to determine if RPD and LPD patients differ in their ability to detect information at the global or local levels. An age- and education-matched normal control (NC) group was expected to show little or no global or local primacy. RPD patients (l-TP, local level, dysfunction) were predicted to demonstrate global primacy, whereas LPD patients (r-TP, global level, dysfunction) would show local primacy. Controlled attention was compared in the same groups and predicted to be impaired in both RPD and LPD patients with inferred l-IPL and right IPL (rIPL) dysfunction, respectively.

Materials and Methods

Participants

20 individuals with LPD (11 women), 18 with RPD (9 women), and 22 healthy normal control (NC) individuals (11 women) who were community volunteers took part in this study. PD patients were recruited from the Parkinson Clinic of the Department of Neurology, Boston Medical Center, the Movement Disorders Clinic at Memorial Hospital of Rhode Island, and local PD support groups; the PD patient volunteers were highly motivated to participate in research studies on PD, and, on average, had attained at least a college education, although these characteristics were not inclusion criteria. There was no difference between the LPD, RPD, and NC groups with respect to age, education, and general cognitive status, with none showing any signs of dementia. Group characteristics are summarized in Table 1. Methods conformed to the ethical standards as described in the 1964 Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Boston University, the Boston Medical Center IRB, and the Committee on Research with Human Subjects at Memorial Hospital of Rhode Island. Written informed consent was obtained from participants prior to their inclusion.

Diagnosis of idiopathic PD, side of disease onset, and disease duration were confirmed by reviewing each PD individual's medical record. Disease duration did not differ between PD subgroups (LPD M= 5.9 years, SD = 3.2; RPD M = 7.1 years, SD = 3.9; t [36] = -1.0, *ns*). A Hoehn and Yahr (H&Y) score for stage of motor disability was provided by each PD patient's neurologist. Frequency of H&Y stages did not differ between PD subgroups (χ^2 [df =4, $\underline{N}$ = 36] = 2.7, *ns*) (Stage *1* = 1 LPD, 0 RPD; Stage 1.5 = 1 LPD, 2 RPD, Stage *2* =14 LPD, 10 RPD; Stage *3* = 3 LPD, 4 RPD, Stage 3.5 = 1 LPD, 0 RPD; note, the H&Y scores were not available for two participants).

All PD participants were taking medication for their parkinsonian symptoms (details not available for one patient). At the time of testing, the motor response was at its optimum ("on" period). Twenty participants followed a medication regimen that included levodopa/carbidopa therapy alone (LPD n=1, RPD n=1), or in combination with one other DA agonist (LPD: n =5; RPD: n = 5), or a DA agonist plus an additional dopaminergic medication (LPD: amantadine, n =2; RPD: amantadine, n =2), or a catechol-O-methyltransferase inhibitor (COMT), (RPD:

n = 3), or an anticholinergic (LPD: *n* = 1). Seven participants were treated with levodopa/carbidopa therapy and the dopaminergic medication amantadine (LPD: *n* =1, RPD: *n* =2) or a monoamine oxidase type B inhibitor (MAO B) (LPD: n = 1, RPD: *n* = 1), or a COMT (RPD: *n* = 2). One LPD participant was treated with levodopa/carbidopa therapy and an anticholinergic. The pharmacotherapy of eight participants did not include levodopa/carbidopa but instead included a DA agonist (LPD: *n* =2), a DA agonist plus a MAO B (LPD: *n*=1, RPD: *n* =1), and a COMT (LPD: *n* =1), or a DA agonist plus an anticholinergic (LPD: *n* =3).

Participants were interviewed about their medical history, including their ophthalmologic health, to rule out confounding diagnoses, such as stroke, head injury, serious medical illness, and ocular/optical abnormalities.

Materials

Stimuli were presented on a 17-inch Studio Display color monitor controlled by a Mac Power G3 computer. The mean luminance of the room (measured at six different locations) was 17.1 cd/m^2. A Cedrus Corporation response box, model 610, was used to collect the data. Hierarchical stimuli were similar to those of Lamb, Robertson, and Knight (1988). Small (local) letters were arranged to form a single large (global) letter (Figure 1). Global letters were 7.4 times as tall as local letters and letters were 1.5 times as tall as they were wide. The local letters subtended approximately 1.2° visual angle vertically and 0.8° horizontally. Global letters subtended about 6.6° visual angle vertically and 4.3° visual angle horizontally. Stimuli were black presented on a light gray background. A set of hierarchical figures were formed from the letters S, H, A, and E. The letters S and H served as targets and the letters A and E served as foils. All possible combinations of these letters appeared equally often with the restriction that every image contained only one target and one foil.

Procedure

Eye-to-monitor distance was approximately 79 cm, which was maintained by having participants use a chin rest for head support. Each trial began with a 500 ms tone. This was followed, 500 ms after tone offset, by a hierarchical pattern presented in the center of the screen until the participant made a response. There was unlimited time to respond. Participants both read and heard instructions asking them to press the “H” key with their index finger whenever they saw an “H”, and the “S” key with their middle finger whenever they saw an “S”, regardless of whether the target letter occurred at the local or global level. All participants were instructed to use their right hand to press the response keys. Only 3 participants (1 LPD, 1RPD, and 1 NC) were left handed, and visual inspection of the mean RTs revealed no differences from the rest of the group. Instructions encouraged participants to respond as quickly and accurately as possible. RTs and errors were recorded.

The attention bias condition was based on the procedures used by Robertson, et al. (1988). The stimuli were presented in three blocks. In the no-bias block, the target “S” or “H” appeared equally often at the each level. In the global-bias block, the target occurred at the global level for 75% of the trials and at the local level for 25% of the trials. The opposite pattern of presentation occurred in the local-bias block.

Stimuli were presented with the following constraints. In the no-bias condition, there could be no more than 4 consecutive same-letter targets, same-letter foils or targets at a single level (local or global). In the global- and local-bias conditions, an additional restriction was such that the first 10 trials appeared at the biased level, which served to direct attention towards that level. No verbal instructions regarding the probabilities were given.

Each participant received a training task and practice trials, as in Lamb and colleagues (1988). Both tasks followed the same presentation constraints as in the no-bias condition. In the training task, participants received written feedback on the monitor about the accuracy of their responses ("That was correct" or "That was incorrect"). All participants completed at least 24 training trials. If necessary, participants were administered additional trials until it was apparent that they understood the response rules. No participant required more than 48 training trials. The practice block consisted of 48 trials without feedback. Participants received 384 experimental trials divided into three blocks of 128 trials each. There was a short break between blocks. Presentation of blocks was counterbalanced across participants. The order of blocks was either global-bias/no-bias/local-bias or local-bias/no-bias/global-bias. To control for the factor of order of presentation of trials, three different orders were created for each local bias, global bias, or no bias condition (i.e., versions A, B, C). Order of the presentation of trials (versions A, B, C) was counterbalanced across participants.

Results

Analyses

Median RTs for each participant were evaluated in separate analyses of the no-bias and attention bias conditions. Errors were not analyzed because the mean error rate was <5% (Mean total errors of five or less per condition). Before the medians were calculated, we removed RTs associated with errors, and very fast RTs (e.g., < 100 ms) that were due to response box limitations. The first ten trials of the biased attention conditions were not included as these trials served to set the biasing condition (Robertson et al., 1988).

For the no-bias condition, to assess the influence of body side of motor symptom onset upon hierarchical pattern perception, RTs were submitted separately to a two-way mixed factorial analysis of variance (ANOVA) with a within-subjects factor of Level (local, global) and a between-subjects factor of Group (LPD, RPD, NC). The effect of biased attention was assessed in a similar three-way mixed ANOVA by adding a within-subjects factor of Bias (global-bias, local-bias).

Order—Separate ANOVAs on RT were conducted to control for an effect of version of stimulus presentation (orders A, B, C) and order of Bias condition presentation (global-bias, no-bias, local-bias *vs*. local-bias, no-bias, global-bias). Both version and order were significant factors in the omnibus analyses (all *p*s <.05, except the Local Bias version, $p<0.1$). Therefore, order and version were considered as between subject factors.

Gender—Because women as a group have been noted to be at a disadvantage on some visuospatial tasks (reviewed in Cronin-Golomb & Amick, 2001), gender was considered as a between-subjects factor in separate ANOVAs on RT. None of these analyses were significant ($p >.80$ in each case). Further analyses consequently collapsed data across gender.

Other Demographics—Both PD subgroups had significantly higher scores on the depression measure of the BDI-II relative to the control group (Table 1). Many symptoms of Parkinson's disease overlap with symptoms of depression, which may account for the significant difference between PD and control participants on the Beck Depression Inventory. In an effort to capture the effect of significant depression symptoms upon HPP participants were dichotomized into depressed or non-depressed (BDI>13). Depression status was considered as a between subjects factor in separate repeated measures ANOVAs on RT, and none of these results were significant ($p >.30$ in each case), and consequently depression was not considered as a between subjects factor. The impact of medication type on HPP was examined. Levodopa/carbidopa and dopamine agonist status (presence *vs*. absence) were

considered as between subject factors. None of these results were significant (all *p*s >.15) and consequently medication was not considered as a covariate.

To examine the contribution of disease severity and performance on the experimental measures, correlations were conducted between RT difference scores, H&Y motor disability scores, and disease duration. We examined the impact of disease severity upon difference scores rather than raw RTs because worsening disease should be associated with slower RTs. Our measure of interest, however, was the comparison of RTs to targets occurring at the different levels (global *vs*. local). Therefore, difference scores (median [*Mdn*] RTs to global targets minus *Mdn* RTs to local targets) were created for each of our experimental conditions (no-bias, global-bias, local-bias). Within the PD group there were no significant correlations between H&Y scores and difference scores for any of the three biasing conditions ($p > .60$ in each case). Similarly, the correlation between disease duration (in years) and the difference scores for each biasing condition was not significant ($p > .30$ in each case). Accordingly, further analyses did not consider these factors.

RT Results

No-Bias—Figure 2a shows the results. Main effect of Group (F [2, 42] = 3.34, p = .05) and Level were significant (F [1, 42] = 4.5, p = .04). The interaction of Level x Group was significant (F [2, 42] = 6.17, p =.004).

Simple effects tests examined further this Level x Group interaction. Between global and local levels, RTs were comparable for the NC group (F [1,16] = 0.26, p =.62), replicating prior findings of level equivalence with this task (Lamb et al., 1988). While the RPD group showed the predicted global precedence numerically, this was not significant (F [1, 12] = 0.39, p =. 55). By contrast, the LPD patients demonstrated an abnormal, local precedence because RTs were significantly slower at the global than local level (F [1,14] = 19.64, p =.001), indicating relatively impaired global level processing.

Between groups, for local level targets, the LPD group had significantly slower RTs than the NC group (F [1, 30] = 12.5, p =.001). The RPD group was numerically but not significantly slower than the NC group (F [1, 28] = 2.58, p =.12). However, RPD and LPD groups did not differ (F [1, 26] = 0.03, p =.87), suggesting that the RPD group like the LPD group was also impaired at the local level. For global level targets, again, the LPD group was slower than the NC group (F [1, 30] = 46.46, p <.001), and the RPD group tended to be slower than the NC group (F [1, 28] = 2.9, p =.098). RTs did not differ significantly between LPD and RPD groups (F [1, 26] = 1.12, p =.30), again, suggesting that the RPD group like the LPD group was also impaired at the global level. In sum, the LPD group (with right hemisphere damage) was impaired at both levels but more at the global than local levels, whereas the RPD group (with left hemisphere damage) showed some evidence of an impairment at both levels like that of the LPD group, but numerically (but not significantly) more at the local than global level.

To examine further if the groups had different RT advantages to either the global or local level, a difference score (global RT minus local RT) was calculated for each participant. The difference scores showed that NC participants responded with comparable speed (difference score =19 ms) to targets occurring at either the local or global level. LPD patients showed local primacy, responding on average 181 ms faster for detecting targets at the local than global level, whereas RPD patients showed global primacy, responding on average 35 ms faster to global than local targets. A one-way ANOVA on difference scores with a between-subjects factor of Group demonstrated a main effect of Group (F [2, 42] = 6.17, p < .005). Three univariate ANOVAs with the between subjects factors of order and version included were conducted to explore this group effect. The scores of the LPD and RPD groups differed significantly (F [1,26] = 9.73, p = .004), and scores of the LPD and NC groups differed

significantly (F [1,30] = 8.5, p = .007), but the scores between the RPD and NC groups did not differ (p = .42). This pattern of results demonstrated that the LPD group showed an abnormal global level precedence that the RPD and NC groups did not show.

Biased-Attention—Figure 2b shows the results. Main effect of Group was not significant (F [2,27] = 0.11, p = .90). Level was marginal (F [1,27] = 2.94, p = .098). The main effect of Bias was significant (F [1,27] = 6.41, p < .02]. The interaction of Group x Level was significant (F [2,27] = 8.22, p =.002). This reflected the observation that overall across both bias conditions, NC and RPD responded faster to global than local targets, whereas LPD showed the opposite, responding faster to local than global targets. This was the pattern observed between RPD and LPD groups under no bias conditions, providing further evidence for this finding. The interaction of Group x Bias was significant (F [2,27] = 6.36, p=.005), as NC and RPD were faster overall under local than global bias, whereas LPD showed the opposite, being faster under global than local bias, regardless of hierarchical level. The LPD effect reflects the observation that this group had comparable RTs in three conditions but much slower RTs to global targets under the condition where attention was biased away toward the opposite, local level (i.e., global targets under local bias), resulting in overall slower RTs under local bias than global bias for only the LPD group. The Bias x Level interaction was significant (F [1,27] = 77.35, p < .0001), confirming the efficacy of our bias manipulation on hierarchical processing. The critical interaction of Bias x Level x Group was not significant (F [2,27] = 0.20, p = .82), suggesting that LPD, RPD, and NC participants were able to benefit from probability information. These results support the significant results and trends found under no bias conditions that LPD patients have problems with global more than local processing, while RPD patients have problems with local more than global processing. The bias manipulation served to exaggerate these processing problems so that the weaker problem in RPD patients could be detected more clearly.

To examine further differences in processing local and global targets in each Bias condition and for each group, we conducted a repeated measures ANOVA on each group and bias condition, separately. Analyses included Global Version and Order as between subject factors. Under global bias conditions, the Level effect was significant for NC (F [1,16] = 8.2, p = 0.01) and tended towards significance in the RPD (F [1,13] = 3.8, p = .07) but not LPD groups (F [1,14] = 0.38, p = .55), as NC and RPD were faster on the biased global target level than the local level, whereas LPD were about as fast at both levels, and even showed the opposite, being slightly slower at the global than local level, suggesting abnormal global processing in LPD.

Under local bias conditions, the Level effect was significant for NC (F [1,17] = 15.7, p = .001) and LPD (F [1,14] = 7.3, p < .02) but not RPD groups (F [1,13] = 0.05, p = .83), as NC and LPD were faster on the biased local target level than the global target level, whereas RPD were about as fast at both levels, and even showed the opposite, being slower at the local than global level, suggesting abnormal local processing in RPD. When attention was biased to the local level, RPD patients were not able to benefit entirely normally from the attentional bias; apparently impaired local level processing in RPD results in RTs that are slower for local than global targets, despite attending to the local level. As a general note, consistent with normal attentional biasing, LPD patients responded faster to global targets, despite impaired processing of them, when presented under global bias relative to under local bias conditions, whereas RPD patients respond faster to local targets, despite impaired processing of them, when presented under local bias than global bias conditions.

To investigate the impact of global or local processing deficits on attentional resources as a function of side of motor symptom onset, the difference score for each participant was compared for each bias condition (global, local). An omnibus, two-way mixed ANOVA on difference scores with a within-subjects factor of Bias and between-subjects factor of Group

demonstrated a significant main effect of Bias (F [1,27] = 77.35. $p < .0001$) and Group (F [2,27] = 8.23, $p = .002$) but not the interaction of Bias x Group (F [2, 27] = .20, $p = .82$).

The differences scores for the local and global biased attention conditions were also compared to each other using repeated measures ANOVA for each group separately with Local/Global Version and Order as between subjects. To determine if differences scores for the separate bias conditions significantly differed from zero, repeated measures within group were run and Order and Version were included as between group factors. To assess group effects, we used a Univariate ANOVA with Group, Version, and Order entered as between subject factors for each pair of groups. For NC, under local bias, a positive direction indicating local precedence was predicted, whereas under global bias, a negative direction indicating global precedence was predicted. If only processing is affected, then RPD should be impaired under local bias (i.e., less positive than NC), whereas LPD should be impaired under global bias (i.e., less negative than NC). If attention or both processing and attention are affected, then PD patients should be impaired in all conditions, showing less biasing in the appropriate direction than NC.

Results for the NC group (who showed no primacy effects in the no-bias condition) revealed that, under local-biased attention, RTs were faster to targets at the local than global level, and this RT change (*Mdn* difference score = 107 ms) differed significantly from zero (F [1, 17] =15.7, $p = .001$). Under global-biased attention, RTs were faster to targets at the global than local level, and this change (*Mdn* difference score = -178 ms) differed significantly from zero (F [1, 16] =8.2, $p = .01$). In sum, the NC group showed RT gains under both local- and global-biased attention conditions. There was a difference between the scores under local versus global bias attention (F [1, 11] =181.5, $p < .001$). These results demonstrate that the NC group benefited significantly from probability information in both biasing conditions.

Results for the LPD group (who demonstrated impaired global level processing in the no-bias condition) revealed that, under local-biased attention, RTs were faster when a local than global target appeared, and this change (*Mdn* difference score = 293 ms) differed significantly from zero (F [1, 14] =7.4, $p = .02$). This RT change in the LPD group tended to differ from that for the NC group (but not RPD [see below]) in this bias condition (F [1, 31] =3.7, $p = .06$), suggesting abnormally large local precedence for the LPD group under locally biased attention. By contrast, under global-biased attention, the LPD group lacked the normal RT advantage for targets occurring at the global relative to local level, and this difference score (*Mdn* = 14 ms) did not differ reliably from zero (F [1, 14] =0.38, $p = .55$). However, the difference between the LPD and NC groups under global bias was not significant (F [1, 30] =0.44, $p = .51$) nor was the difference between the LPD and RPD group (F [1, 27] =1.05, $p = .31$). In sum, the LPD group showed an RT gain under local but not global attention bias conditions, unlike the NC group who showed a gain under both. Like the NC group, the LPD group showed that difference scores under global versus local bias attention differed significantly (F [1,8] = 14.68, $p = .005$), but, for the LPD group, it was because they showed an RT advantage for probability information provided at the local level, but when attention was instead biased to the global level, the RT benefit for global level targets did not occur. Taken together with the finding of abnormally worse global than local processing in LPD under no-bias conditions, this pattern of bias attention findings provide further support for an LPD impairment at global more than local level processing.

The opposite pattern of results was obtained for the RPD group, who had appeared to show impaired local level processing in the no-bias condition. Under local-biased attention, unlike both NC and LPD groups, the RPD group lacked the normal RT advantage for targets occurring at the local relative to the global level, and this difference score (*Mdn* = -39 ms) did not differ reliably from 0 (F [1, 13] =0.05, $p = .83$). While the comparison of difference scores between RPD and NC groups did not reach significance (F [1,30] = 2.83, $p = .10$), the RPD pattern did

differ significantly from the LPD group, who did show a normal RT advantage in this condition (F [1,27] = 6.74, p = 0.02), indicating the RPD group did not show a normal pattern under these conditions. This result demonstrates a single dissociation for local level processing in the RPD group. Under global-biased attention, the RPD group demonstrated slower RTs to local than global targets, and there was a trend for this RT change to be significant (*Mdn* difference score = -250 ms) (F [1, 13] =3.8, p =.07), and this global bias pattern did not differ reliably from that of the NC group (F [1,29] = .01, p = .92), suggesting relatively normal global level processing in RPD, and providing evidence for a double dissociation, though the RPD and LPD patterns did not differ (F [1,27] = 1.05, p = .31). The RPD group seemed to show an RT gain under global but not local attention bias, unlike the NC group who showed a gain under both, and, indeed, in the RPD group, difference scores under global versus local bias differed significantly (F [1,8] = 19.48, p = .002). In sum, the RPD group showed the opposite RT pattern relative to the LPD group who benefited from local but not global attention bias. The RPD results demonstrate clearly that these patients benefited when attention was biased to the global level but to a lesser extent when attention was biased to the local level.

The difference scores provided evidence that the NC group but neither PD group showed comparable bias effects under local and global attention. In particular, the LPD group exhibited a clear benefit of local bias but not global bias of attention on local processing, consistent with the global processing impairment demonstrated under no-bias conditions. By contrast, the RPD group showed a greater benefit of global bias than local bias of attention on global level processing, consistent with the local processing problems suggested under no bias conditions.

Discussion

The findings demonstrate that LPD and RPD patients show opposite patterns of abnormal perceptual processing of hierarchical patterns, despite normal ability to control attention between levels. Overall, PD patients are highly accurate (> 95% correct), but tend to be generally slower to respond to any hierarchical visual pattern, which is expected due to general slowing of processing related to their basal ganglia dysfunction. To test our hypotheses requires examining how processing differs between global and local levels. Their response speed demonstrates a pattern of visuospatial processing dysfunction that differs depending upon side of motor symptom onset. As predicted, RPD and LPD patients show a pattern of performance that resembles patients with unilateral lesions in the left or right TP, respectively. LPD patients with hypothesized r-TP dysfunction showed a clear single dissociation: Abnormal processing of the global level of hierarchical visual patterns (i.e., abnormal local primacy), regardless of the focus of attention. By contrast, RPD patients with hypothesized l-TP dysfunction showed the opposite: Impaired processing of the local level (i.e., abnormal global primacy), but this processing deficit occurs mainly when attention is biased toward one level. This overall pattern of findings supports our hypothesis, which emphasizes relative dysfunction between hemispheres: LPD patients show visuospatial impairments reflecting greater right hemisphere dysfunction, and RPD patients show visuospatial problems reflecting greater left hemisphere dysfunction. The present evidence suggests a dissociation such that global more than local processing is abnormal in LPD, whereas local more than global processing is abnormal in RPD, but RPD patients have this problem mainly when attention is biased toward one level or the other. Taken together, these findings demonstrate that (1) PD patients have visuospatial impairments; (2) these impairments appear to be related to dysfunction in a neural pathway that includes brain regions important for visuospatial abilities (i.e., posterior temporal-parietal junction and/or a basal ganglia - TP pathway); and (3) RPD and LPD patients produce opposite patterns of abnormal visuospatial processing when tested with hierarchical figures.

Visuospatial Perception

Two previous studies have compared the performance of PD patients on processing targets at the global and local levels with conflicting results. Filoteo and colleagues (1994) found that PD patients did not differ from control participants in their ability to detect targets at the global or local levels, whereas Barrett and colleagues (2001) reported that PD participants show a global processing deficit. A possible reason for this discrepancy may be body side of motor symptom onset, but neither study reported this important patient characteristic. Consider that, in the current experiment, LPD patients demonstrate a processing deficit at the local more than global level, whereas RPD patients have problems more at global than local level processing, though mainly when attention is biased toward one level. It is possible that the contradictory findings of Barrett et al. (2001) and Filoteo et al. (1994) could be reconciled by analyzing side of motor symptom onset of their samples. For example, averaging across RPD and LPD groups, who are normal at one level or the other, might produce a null effect, such as was reported by Filoteo et al. (1994), whereas a preponderance of LPD patients might produce a global processing deficit, such as was reported by Barrett et al. (2001). The present study emphasizes the importance of considering the critical factor of body side of motor symptom onset when interpreting PD performance on cognitive tasks requiring lateralized brain functions.

Attention

We found that unlike l-IPL patients, the LPD and RPD groups were able to benefit from probability information. When attention is biased to favor the processing level corresponding to their relatively intact hemisphere, both PD groups show normal RT benefits for their intact processing level: LPD patients show normal local precedence under local bias, and RPD patients show normal global precedence under global bias of attention. Notably, all groups show a substantial 100 to 300 ms biasing effect, at least under conditions when biasing effects were obtained in a particular PD group.

This finding differs from that of Filoteo and colleagues (1994), who reported that attention to hierarchical levels is disrupted in PD. In a no-bias condition where targets occurred at the local or global level with equal probability, they examined the influence of the previous trial on the succeeding trial. In two consecutive trials where the target occurred at the same hierarchical level, healthy adults demonstrated a RT benefit or priming effect (i.e., RTs were faster on second trials). By contrast, when the target switched levels between successive trials, there was a RT cost (i.e., RTs were slower on second trials). PD participants had reduced benefit and cost effects: They did not show as great an RT benefit when the target stayed at the same hierarchical level, and they showed a reduced cost when the target switched between levels. The authors proposed that the ability to maintain attention to a specific target is disrupted in PD. This conclusion appears to conflict with the finding in the current study that PD patients were able to allocate their attention to a particular level of the hierarchical figure based on probability information, at least for the hierarchical level at which their processing was normal or nearly so. In addition, we replicated the analyses of Filoteo and colleagues (1994) with almost all of our dataset (17 LPD, all RPD, 21 NC), and found no significant RT cost-benefit effects between the three groups ($p<0.15$).

One potential explanation for these contradictory findings could be differences in the methods used to assess attention. Using an unbiased attention condition, Filoteo et al. (1994) measured the impact of the proceeding trial upon RTs. The current study, using a biased attention condition, measured changes in RT based on adjusting the probability that the target would occur at a particular level. This explanation, however, is rendered unlikely by findings of Robertson and colleagues (1993) with healthy college-aged adults. They reported that in both biased and unbiased conditions, attention to a particular level is set before trial onset and is linked to the attended level of the previous trial.

Another possibility is differences in participant characteristics. In the current study, PD participants were at a relatively early stage of the disease (mainly H&Y stage 2), whereas participants in Filoteo and colleagues' (1994) study were in the later stages of PD (mainly H&Y stages 3-4). The neuropathology of PD involves additional brain structures with disease progression, which may result in the attentional problems seen in patients with more advanced disease.

Functional Neuroanatomy and Cognition

Neuropathology of PD disrupts HPP—The present findings provide evidence that the connections between the basal ganglia and the brain areas at the posterior temporal-parietal junction, important for HPP, are disrupted in PD. Current understanding of corticostriatal circuits based on monkey neuroanatomy suggest closed corticostriatal loops from cortex to striatum and then to the globus pallidus or substantia nigra, output nuclei of the basal ganglia, and back to cortex via the thalamus (Alexander, DeLong, & Strick, 1986). While evidence for frontostriatal and temporostriatal loops has been established (Middleton & Strick, 2000a,b), evidence for a posterior parietal loop is continuing to emerge. So far, the anterior intraparietal region (AIP, area 7b, area PF) has been shown to project to the ventral putamen and sparse parts of the caudate head and body in the basal ganglia (Yeterian & Pandya, 1993). In turn, the SNpr projects back to area AIP via the thalamus (Clower et al., 2005), perhaps forming the output channel for a posterior parietal loop (Middleton & Strick, 2000a). This disynaptic projection has been proposed as an anatomical basis for observations of visuomotor and visuospatial cognition deficits in PD patients that resemble those observed in patients with posterior parietal damage (Clower et al., 2005). The present findings that HPP, which depends upon posterior parietal but not DLPFC areas, is impaired in PD favors the idea that basal ganglia-posterior parietal connections, and not a frontostriatal loop, underlies this visuospatial problem in PD.

It is as yet unclear which monkey areas correspond to the TP (posteroventral parts of BA 39/49, and posterior BA 22/37) and IPL (BA 39/40) areas implicated in HPP and attention, respectively. Homologies are problematic for various reasons (Sereno & Tootell, 2005) including the expansion of parietal cortex outside of topographically organized regions in humans relative to monkeys and findings that some parietal regions, including parts of human intraparietal sulcus, are present in humans but not monkeys (Van Essen et al., 2001; Vanduffel et al., 2002). Nevertheless, the most likely monkey homologues may be those projecting primarily to the caudate, the part of the striatum implicated in cognition.

Human IPL and TP regions implicated in HPP and perception may reflect relatively more dorsal versus more ventral functional subdivisions, respectively, of posterior parietal areas in nonhuman primates. At the most dorsal end, area LIP has been implicated in determining stimulus salience and rapid orienting of attention (e.g., Bisley, Krishna, & Goldberg, 2004), and projects to centrolateral parts of the head and body of the caudate. At the most ventral end, area PG-Opt at the most caudal part of the monkey inferior parietal lobe at the tip of the superior temporal sulcus, has been implicated in visuospatial functions and projects to the dorsal parts of the head and body of the caudate (Blatt, Pandya, & Rosene, 2003; Yeterian & Pandya, 1993). In between is area 7. Area 7a has been implicated in visuospatial cognition and attention (e.g., Constantinidis & Steinmetz, 2005; Crowe, Chafee, Averbeck, & Georgopoulos, 2004) and projects to the entire caudate (Cavada & Goldman-Rakic, 1991; Yeterian & Pandya, 1993). A part of area 7b, area AIP, is the one parietal region to date that has been shown to receive input from the SNpr (Clower et al., 2005). The potential human homologue of this region in caudal intraparietal sulcus has been implicated in the important visuospatial function of object perception and grasping, storing representations of tools, and computing the relative spatial relations between object features (Chao & Martin, 2000; Grezes, Armony, Rowe, &

Passingham, 2003; Schendan & Stern, 2007; 2008). Since we found no evidence for impaired attentional biasing during HPP in PD, which is thought to depend upon l-IPL (Robertson et al., 1988), the basal ganglia may not play an important role in attentional biasing of perception. However, a previous study reported abnormal attention in patients with later disease stages (Filoteo et al.1994), suggesting that basal ganglia mediated attention abilities can be affected later on as PD progresses. Therefore, we cannot rule out that the intact performance in our early PD group was due to sparing of the relevant corticostriatal pathway at this earlier stage of the disease.

The projections involving the IPL and TP would be vulnerable to disruption in PD based on the location of their terminations within the striatum and the corresponding DA loss in PD. Postmortem neurochemical analysis has shown uneven patterns of striatal DA loss in patients who died of idiopathic PD (Kish, Shannak, & Hornykiewicz, 1988). The dorsal and intermediate zones of the putamen had the greatest loss of DA, and this pattern of loss was found in both early and late stages of the illness. Though the caudate was overall less affected than the putamen, depletion of DA in the head of the caudate was profound, with less than 4% remaining compared to non-PD samples. Thus, the severe loss of DA in the putamen and head of the caudate nucleus, even at the earliest stages of PD, is likely to disrupt cognitive processes (e.g., analyzing hierarchical levels) that depend upon a basal ganglia pathway involving the human IPL and TP. The severe and asymmetrical loss of DA in these basal ganglia regions even in the early stages of the disease might explain why LPD and RPD groups who were in the relatively early stages of the disease have global and local processing deficits, respectively.

Basal Ganglia and Parietal Dysfunction and Spatial Cognition—In general, dysfunction in either parietal cortex or a basal ganglia-parietal pathway can cause spatial cognition problems. Using nearly identical methods, we have observed a pattern similar to the present RPD results with HIV+ relative to HIV-groups: HIV+ patients also show a local processing problem that is revealed most clearly under global bias attention (Olesen, Schendan, Amick & Cronin-Golomb, 2007). We hypothesized that this finding reflects known parietal-lobe dysfunction in this disorder. We have also found evidence for visuospatial deficits using the cardinal visuospatial task of mental rotation but only when the stimuli were hands (Amick et al. 2006), a task version that entails visuomotor transformation and additionally recruits motor cortex (Ganis, Keenan, Kosslyn, & Pascual-Leone, 2000). For hand rotation, we found evidence for a double dissociation between LPD and RPD groups depending upon visual field presentation: While LPD patients were impaired when mentally rotating hands on the left, RPD patients were impaired with hands on the right. Many of the same PD patients in this mental rotation study were also included in the present study. Comparisons between results on mental rotation and HPP with the same subgroup of PD patients show that the general finding of visuospatial deficits as a function of side of motor symptom onset is obtained on both tasks. This finding indicates that different visuospatial tasks that depend upon different parts of the posterior parietal lobe show different patterns of performance depending upon body side of PD onset. In general, cognitive abilities that depend upon any posterior parietal region, especially those with lateralized parietal involvement, and that have task characteristics that recruit the basal ganglia will probably show patterns of impaired performance in PD that vary with side of disease onset.

The present findings suggest a link between side of motor symptom onset in PD and hemispheric asymmetry of an inferior parietal - basal ganglia pathway involving the TP and caudate head that is necessary for the visuospatial ability of hierarchical pattern perception. However, our results cannot determine whether HPP is affected because the TP is part of a neural pathway involving the basal ganglia regions affected in PD, or because PD causes dysfunction in the TP itself, or both. Neuroimaging evidence may address this, but most studies to date focus on more behaviorally impaired groups and do not examine motor symptom

lateralization. Consequently, there is little direct evidence that activity in TP in particular is abnormal in non-demented early PD, particularly with side of onset considered, but some suggestive evidence has been found. Hypoactivation in the posterior superior temporal gyrus, which overlaps the TP region implicated in HPP, has been found during visual cognitive tasks in non-demented PD patients with normal executive function relative to control participants, some of whom were tested in the present study (Tinaz, Schendan, & Stern, 2008). However, this finding did not differ with side of onset, though this could be due to the small LPD and RPD group sizes (Tinaz et al., 2008). Lateralized parietal dysfunction is possible as white matter atrophy has been found in the left parietal lobe in PD patients with executive function problems (Matsui et al., 2007). Future neuroimaging work will be needed to clarify whether the TP region itself is affected in PD and in a lateralized manner, or whether problems on visuospatial tasks involving the TP reflect dysfunctional parieto-basal ganglia interactions due primarily to abnormal neural processes originating in the basal ganglia. Nonetheless, given the known, severe basal ganglia neuropathology in PD, the primary dysfunction likely arises in the basal ganglia, which then disrupts processing along a lateralized parietal-basal ganglia pathway recruited for HPP.

In general, cortical-basal ganglia interactions seem to play a causal role in context-dependent selection of patterns of perceptual, cognitive, or motor activity that are salient or behaviorally relevant given current task goals and environmental context (Brasted & Wise, 2004; Cools, Clark, & Robbins, 2004; Cromwell & Schultz, 2003; Lawrence, Watkins, Sahakian, Hodges, & Robbins, 2000; Williams, Rolls, Leonard, & Stern, 1993). The role of the striatum in cognition may be to transform cortical representations of perceptual, memory, or motor information into a representation that is appropriate for the specific behavioral context (Johnstone & Rolls, 1990; Lawrence et al., 2000). Each striatal neuron receives convergent input from multiple cortical columns and so may classify patterns of neural activity across a broad functional region (Cheng, Saleem, & Tanaka, 1997) with the function of the striatal and cortical components determined by the respective functions of each (Yeterian & Pandya, 1991). For example, neurophysiological studies (Brasted & Wise, 2004) have demonstrated parallel and simultaneous learning-related activity in both the cortical and striatal structures of a loop (e.g., premotor cortex and putamen). Also, a closed temporostriatal loop involves monkey area TE along the ventral visual pathway for shape and color processing, which both receives input from and sends output to the basal ganglia (Middleton & Strick, 1996; Van Hoesen, Yeterian, & Lavizzo-Mourey, 1981; Yeterian & Pandya, 1995), and, accordingly, both area TE and the caudate tail show strong visual stimulus selectivity, large bilateral receptive fields, visual location constancy, and repetition suppression (Brown, Desimone, & Mishkin, 1995). Most important here, as we suggested, evidence is accumulating that posterior parietal cortex is also part of a closed corticostriatal loop (Clower et al., 2005). If so, then the part of the caudate that is the basal ganglia component of the posterior parietal loop will have functional properties similar to its cortical counterpart. The role of this caudate region in perception and attention during the HPP task might be to transform the spatial representations in the TP into a representation that can be used for response selection, with the basal ganglia enabling more rapid selection of patterns of perceptual, cognitive, or motor activity that are salient or behaviorally relevant given current task goals, and consistent with the well-known role of the basal ganglia in acquiring stimulus-response mappings for diverse kinds of implicit learning tasks (e.g., Ashby & Maddox, 2005; Schendan, Searl, Melrose, & Stern, 2003). The particular role of the basal ganglia will depend upon the role of the corresponding cortical region in accomplishing the task goals.

Conclusions

Early stage LPD and RPD patients show a pattern of performance on HPP that resembles that seen in individuals with unilateral lesions in the r-TP or l-TP, respectively, but not the

attentional control problems seen in patients with l-IPL lesions. Patients with LPD have abnormal global processing, like r-TP patients, regardless of the focus of attention. Patients with RPD have the opposite, abnormal processing of the local level, like l-TP patients, except that the local processing problem in RPD is evident mainly when attention is biased toward the problematic local level. When attention is biased to the global or local level, RPD and LPD patients can benefit from probability information, respectively, and, in this respect, do not resemble patients with lesions in the l-IPL. These findings emphasize that future research on the cognitive abilities of patients with PD must consider the factor of side of motor symptom onset. Disregarding this important aspect of the disease could lead to null findings, which may mask or minimize the true prevalence and nature of spatial dysfunction in the PD population.

These findings, which demonstrate that PD patients are impaired on a visuospatial task that has been shown to depend only on the TP and not the DLPFC, suggest that a lateralized pathway between posterior parietal cortex and the basal ganglia have a necessary role in HPP. Prior neuropsychological evidence has identified TP but not the DLPFC as necessary for HPP (Robertson et al., 1991). As we found abnormal HPP in PD, visuospatial dysfunction in PD can reflect dysfunction primarily in a posterior parietal-basal ganglia network and not a DLPFC-striatal loop; we note though that PD-related parietal damage, irrespective of basal ganglia damage, may also contribute. Given this, our finding of opposite dissociations in LPD *versus* RPD on HPP, especially under conditions of biased attention, indicates that connections between the TP and the basal ganglia (Middleton & Strick, 2000a,b; Clower et al., 2005) may be critical for the visuospatial ability of HPP. We propose that HPP tasks require the recruitment of a lateralized TP-basal ganglia network, perhaps even a parietostriatal loop. This neural network enables the selection of the appropriate local or global visual level at which a target pattern occurs in order to achieve the task goal and rapidly select a response. These findings add to the growing list of visuospatial abilities that depend upon cortical-basal ganglia connections and are important not only for theoretical understanding of the role these interconnections have in cognition but also for characterizing the range of visuospatial impairments in PD.

Acknowledgments

Drs. Amick and Schendan shared equally in this research endeavor, and share first authorship. This work was supported by the National Institute on Aging (NIA) grant T32AG00220 to the Boston University Gerontology Center, by a Grant-in-Aid of Research from Sigma Xi and by a Clara Mayo Research Award from the Department of Psychology, Boston University (M.M.A.), and by the National Institute on Aging, National Research Service Award F32-AG005914, National Institute of Mental Health R21 Grant MH66213, and Tufts University start-up funds (H.E.S.), and by National Institute of Neurological Disorders and Stroke R01 Grant NS052914 (A.C.G.). The study was presented in part at the annual conference of the International Neuropsychological Society, 2004. We thank all of the individuals who participated in this study. We are also grateful to Marie Saint-Hilaire, MD, Terry Ellis, MSPT, NCS, and Cathi Thomas RN, MS, for aiding us in our recruitment efforts, John Gittinger, MD, for conducting the neuro-ophthalmological examinations, Sandra Neargarder, Ph.D. for consulting on statistical analyses, Sigurros Davidsdottir, PhD, Uraina Clark, PhD, and Kristine Hanna, PhD, for assistance in data collection, and Tom Laudate, MA, and Helen Tretiak-Carmichael, MA, who provided expert technical support.

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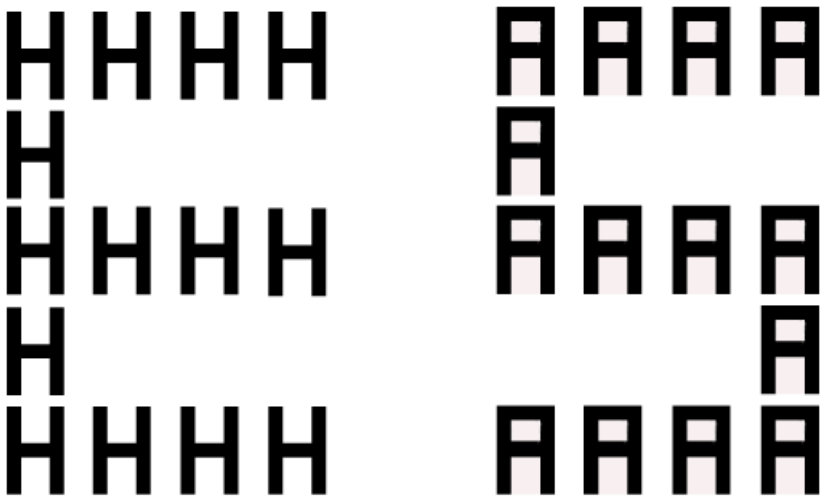

Figure 1.
Hierarchical Stimuli. A: Small (local) letter “H”s were arranged to form a single large (global) letter “E”. The target is the letter “H” and the foil is the letter “E”. B: Small (local) letter “A”s were arranged to form a single large (global) letter “S”. The target is the letter “S” and the foil is the letter “A”.

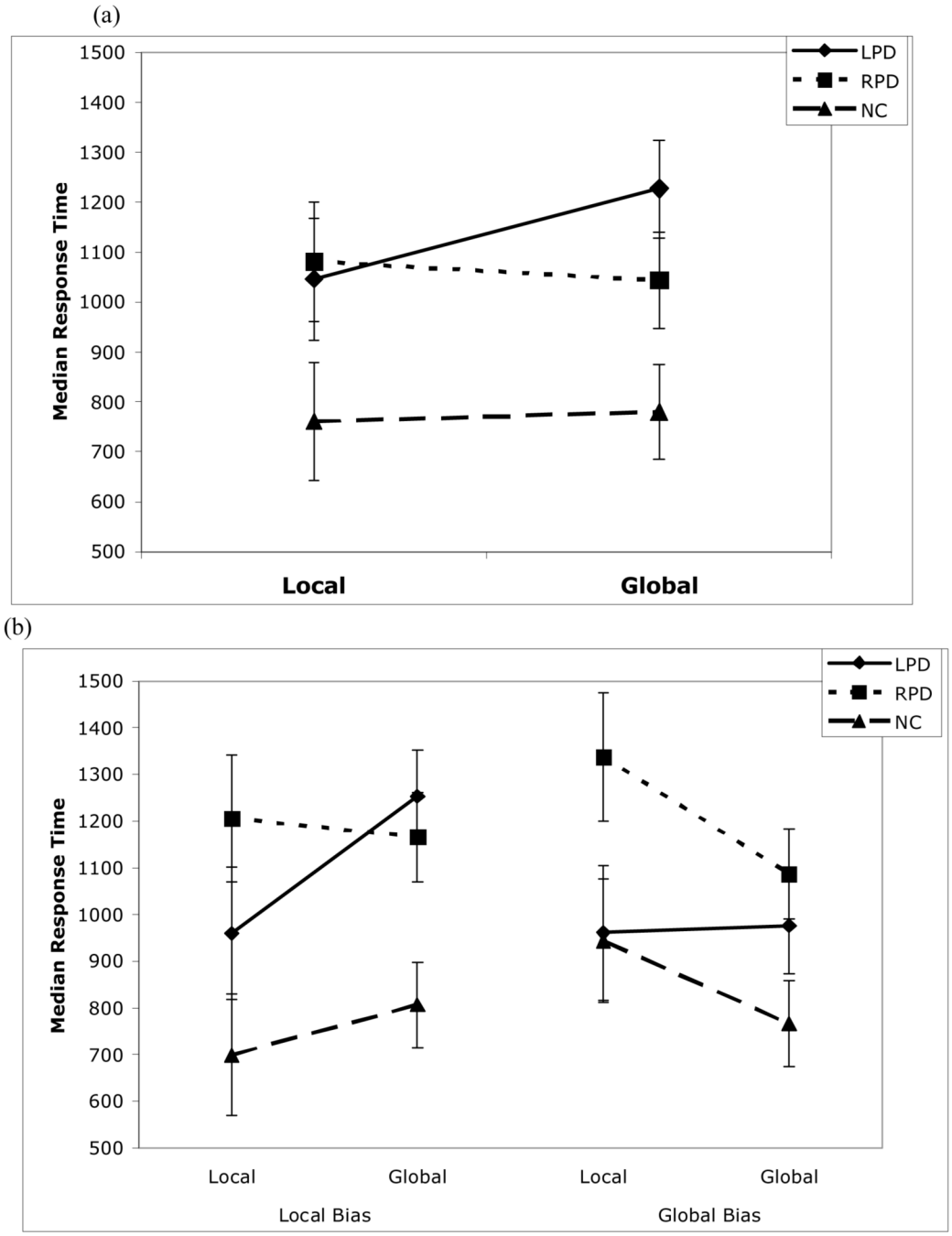

Figure 2.

(a) Median RTs (ms) for the LPD, RPD, and NC groups in the no-bias condition. (b) Median RTs (ms) for the LPD, RPD, and NC groups in the biased-attention conditions. The left half of the graph represents median RTs to targets occurring at the global or local levels in the local-biased attention condition. The right half of the graph represent median RTs to targets occurring at the global or local levels in the global-biased attention condition.

Table 1

Group characteristics

	Group	Mean	SD	Range	*F*	*p*
Age	LPD	60.35	7.06	45-84	1.68	*ns*
	RPD	65.06	9.87			
	NC	64.48	9.22			
Education	LPD	16.45	3.02	12-21	1.37	*ns*
	RPD	16.56	2.64			
	NC	17.71	2.43			
MMSE	LPD	29.2	0.99	27-30	0.63	*ns*
	RPD	29.2	0.86			
	NC	29.4	0.81			
BDI-II	LPD	9.00	6.79	0-27	10.32	<0.001
	RPD	10.39	5.67			
	NC	3.14	3.03			

LPD: Left body side of motor symptom onset, RPD: Right body side of motor symptom onset, NC: Normal Control, MMSE: Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), DRS: Dementia Rating Scale (Mattis, 1988), BDI-II: Beck Depression Inventory.