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Ocular motor ability and covert attention in patients with Duane Retraction Syndrome

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ABSTRACT

Is orienting of spatial attention dependent on normal functioning of the ocular motor system? We investigated the role of motor pathways in covert orienting (attentional orienting without performing eye movements) by studying three patients suffering from Duane Retraction Syndrome—a congenital impairment in executing horizontal eye movements restricted to specific gaze directions. Patients showed a typical exogenous (reflexive) attention effect when the target was presented in visual fields to which they could perform an eye movement. This effect was not present when the target was presented in the visual field to which they could not perform eye movements. These findings stress the link between eye movements and attention. Specifically, they bring out the importance of the ability to execute appropriate eye movements for attentional orienting. We suggest that the relevant information about eye movement ability is provided by feedback from lower motor structures to higher attentional areas.

1. Introduction

In daily life we are required to move attention to points of interest around us. Such movements of attention are strongly coupled with eye movements. Namely, except for specific situations (such as making a "no-look pass" during a basketball game or trying to inspect someone's behavior without attracting his attention), our attention is usually directed to the center of our gaze. However, it is possible to shift attention covertly without eye movements (Posner, 1980). This work examines the linkage between attentional covert orienting and eye movements.

In order to orient attention to a point of interest we use two different mechanisms—exogenous (reflexive) and endogenous (volitional) orienting. Both exogenous and endogenous orienting can be measured using Posner's cueing task (Posner, 1980). In this task participants are presented with three horizontally aligned squares (Fig. 1). They are required to press a button as soon as they detect the appearance of a target preceded by a spatial cue. Researchers commonly use a central cue (usually an arrow) that predicts target location to produce endogenous orienting of attention, or a peripheral cue (usually a brief brightening of one of the peripheral squares), which does not predict target location, to produce exogenous orienting of attention. It is important to note that this task measures covert attention. Namely, participants perform the task without moving their eyes.

The typical pattern of results in an exogenous spatial cueing task (Posner & Cohen, 1984) is an early validity effect followed by inhibition of return (IOR). That is, reaction time (RT) for valid trials (i.e., target and cue appear at the same location) is faster than for invalid trials (i.e., target and cue appear at different locations) at short cue-target intervals (SOA—stimulus onset asynchrony), and slower for valid than for invalid trials at longer SOAs. In contrast, endogenous cueing produces a validity effect for all SOAs.

Is attention dependent on ocular motor functioning? The connection between motor operation and attentional allocation is the focus of a long standing debate. According to the premotor theory (Rizzolatti, Riggio, Dascola, & Umilta, 1987), attentional allocation is created by the programming of eye movement. The premotor theory has been supported by several works. Rafal, Calabresi, Brennan, and Sciolto (1989) demonstrated that preparation for eye movements can produce IOR even with endogenous orienting. Several reports have indicated the importance of the superior colliculus (SC), a subcortical structure involved in the programming of eye movements, in IOR (Berger & Henik, 2000; Rafal et al., 1989; Ro, Shelton, Lee, & Chang, 2004; Sapir, Soroker, Berger, & Henik, 1999). However, some findings supporting the premotor theory were later contested (Dori & Henik, 2002).

Several works have examined the influence of ocular motor disability on attentional allocation. Craighero, Carta, and Fadiga (2001) have examined the influence of peripheral sixth nerve palsy on endogenous orienting of attention. The patients in this study

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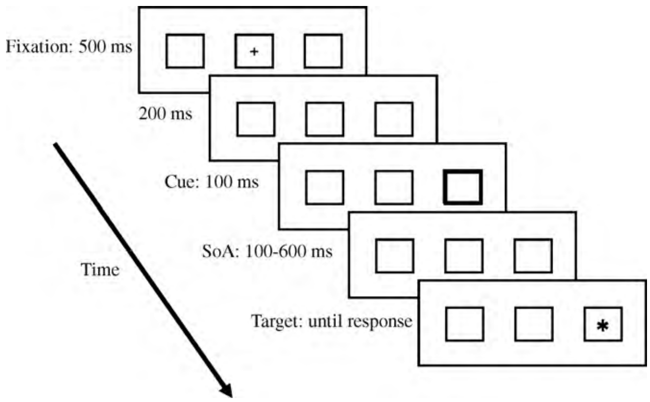

Fig. 1. A typical experimental trial of the exogenous orienting task.

suffered from acute horizontal binocular diplopia and unilateral eye movement limitation. These patients showed a normal validity effect when viewing with the healthy eye, but no validity effect viewing with the affected eye.

Although the premotor theory focused on endogenous attentional orienting, there have been some indications of a connection between exogenous attention and eye movements. Smith, Rorden, and Jackson (2004) presented a patient who suffered from a congenital condition that prevented her from making eye movements. The patient did not present a validity effect in an exogenous orienting task, although she showed a robust endogenous validity effect (in contrast to the patients of Craighero et al., who demonstrated a deficit in endogenous orienting). The authors suggested that the lack of a validity effect in exogenous orienting was a product of an undeveloped attentional system. However, it is possible that the attentional system was properly developed and the lack of a validity effect was due to a malfunctioning motor system essential for proper orienting of attention. We tested this hypothesis in the current work.

2. The current work

In this work we examined the attentional abilities of three patients with Duane Retraction Syndrome (DRS). DRS is a congenital eye movement disorder characterized by a failure of cranial nerve VI (the abducens nerve) to develop normally, resulting in unilateral or bilateral restriction or absence of abduction, adduction, or both, narrowing of the palpebral fissure and retraction of the globe on attempted adduction, as well as an occasional upshoot or downshoot in adduction (Duane, 1905).

3. Materials and methods

3.1. Participants

Three patients with DRS (all female, RP aged 26, GS aged 16, and SH aged 30 years) and 20 age-matched control subjects (16–27 years old) participated in the experiment. Control subjects received course credit from Ben-Gurion University of the Negev or payment for their participation.

Patient RP was diagnosed with left DRS in early childhood due to strabismus and a head turn. In an attempt to correct her ocular motility, RP had two strabismus surgeries, at age 6 years for horizontal misalignment and at age 17 years for vertical misalignment (upshoot of the left eye). At the time of testing she still had a severe limitation of abduction of her left eye, which could not cross the midline. She also exhibited a mild limitation of adduction, as well as narrowing of the palpebral fissure and retraction of the globe on attempted adduction of this eye. At the time of testing, RP did not have horizontal strabismus while looking straight-ahead, but still exhibited an upshoot of the left eye in adduction, causing a 6 prism-diopters hyperdeviation of this eye. She had no limitation of right eye movements. Although RP recalled having occasional diplopia in childhood, she did not have diplopia after the strabismus surgeries.

Patient GS was also diagnosed with left DRS in infancy due to limited movements of the left eye and occasional left head turns. She did not have strabismus when gazing straight-ahead and never had extraocular muscle surgery. GS had a limitation of abduction of the left eye beyond the midline and narrowing of the palpebral fissure on attempted adduction of this eye. No limitation of adduction or vertical eye muscle imbalance was found. Right eye movements were normal. GS reported diplopia in the extreme left gaze, but did not experience diplopia during testing.

Patient SH has had limitation of eye movements since early childhood, but did not seek medical attention until 3 months before testing, when she was diagnosed with bilateral DRS. She had no strabismus on a straight-ahead gaze and has not had any eye muscle surgery. There was a moderate limitation of abduction of both eyes and mild narrowing of the palpebral fissure on attempted adduction of each eye. SH had an over action of both inferior oblique muscles, more significant on the left side, and no limitation of adduction. She reported occasional diplopia on lateral gazes but not on a straight-ahead gaze, and did not experience diplopia during testing.

All patients had normal uncorrected visual acuity (20/20) in each eye and could perform the testing task without difficulty. The control subjects were healthy participants with no known ocular motor pathology.

Patients and control subjects performed an exogenous and endogenous cueing task, except for SH who performed only the exogenous task.

3.2. Apparatus and stimuli

3.2.1. Exogenous cueing

The stimuli were white figures, on a black background, consisting of a fixation plus sign (size 0.3°) at the center of a computer screen, and three horizontally aligned square boxes (2.5° each side), one located at the center of the screen, and the other two were 6.5° from it (Fig. 1). A target asterisk (1.3°) appeared in the center of one of the peripheral boxes. It was preceded by a brightening of one of the two peripheral boxes, which was accomplished by widening the box's contour from 1 to 5 mm. Participants responded to the asterisk by pressing the space bar of a keyboard.

Participants were tested in a dimly illuminated room. They were seated 57 cm from the computer monitor and performed the task using a chin rest. Participants wore glasses or contact lenses during the testing if needed for clear vision. After 1000 ms from the beginning of a trial, a fixation plus sign appeared for 500 ms. Participants were instructed to maintain fixation on the plus sign location throughout the experiment. The experimenter monitored eye movements of patients RP and GS, as well as of the control individuals, through a JVC-TK240 video camera. If an eye movement was detected, the experimenter sent an alerting sound to the participant. Eye movements of patient SH were recorded using a video-based desk-mounted eye tracker (EyeLink 1000, SR Research, Ontario, Canada) with a sampling rate of 1000 Hz. Two hundred milliseconds after the disappearance of the fixation plus, there was a brightening of one of the two peripheral boxes (the cue) for 100 ms. One hundred, 300 or 600 ms after the onset of the cue, the target appeared in one of the peripheral boxes and remained in view until participants responded (Fig. 1). The cue was not predictive as to where the target would appear. Each participant completed the experiment twice, each time with a different eye covered by an eye patch. The order of eyes being tested was counter balanced between participants. The participants were instructed to press the space bar as fast as possible when the asterisk appeared, but to avoid false responses. They were informed that the peripheral cue was not informative as to where the target would appear. Each experiment included 212 trials (16 for each validity condition, target location and SOA), of which 20 were catch trials where the target did not appear and participants were instructed not to respond. Each experiment began with 8 practice trials.

The ethics committee of Ben-Gurion University of the Negev approved the study and all participants gave written informed consent.

3.2.2. Endogenous cueing

In the second experiment, endogenous spatial attention was tested. This experiment was similar to the first experiment except for the following differences: (1) instead of a peripheral cue we used an arrow that pointed to the target location in 80% of the trials, and (2) the experiment contained 528 trials (64 valid and 16 invalid trials for each SOA and target location condition), with an additional 48 catch trials.

4. Results

Three patients with DRS were tested: GS with limitation of abduction of the left eye, RP with impaired abduction and adduction of the left eye, and SH with limited abduction of both eyes. All patients and control subjects performed an exogenous cueing task. Two patients, RP and GS, as well as control individuals, also performed an endogenous task. These two patients and the control group were tested while monitoring their eye movements using a video camera. To better evaluate the effect of eye movements during the test, patient SH was recorded using a video-based desk-mounted eye tracker (EyeLink 1000).

Data of patients RP and GS were analyzed in comparison to that of control individuals. For each patient, we conducted two separate four-way ANOVAs (analysis of variance), one for the patient and the other for their control group. Each analysis was for eye (left and right) × validity (valid and invalid) × SOA (100, 300 and 600 ms) × target visual field (right and left). We also used the procedure of Crawford and Garthwaite (1998) (Crawford, Garthwaite, Howell, & Gray, 2002) in order to compare the validity effect between the patients and the control group. For patient SH we conducted a four-way ANOVA, for visual field (accessible and inaccessible) × eye (left and right) × validity (valid and invalid) × SOA (100, 300 and 600 ms).

4.1. Patient RP

In the exogenous task, there was a significant difference in RPs validity effect at the first SOA, between the two eyes ($P = 0.014$, see Supplement 1-a). Specifically, when viewing with her right eye RP showed the typical validity effect and IOR, although when viewing with the left eye no validity effect was present (see Fig. 2). This was a result of a slowed response to valid trials in the inaccessible visual field ($P = 0.003$, see Supplement 1-a). For the control sample the typical validity effect and IOR were observed and were not modulated by the viewing eye.

Comparison of RPs validity effect to that of the control subjects showed a significant difference between RPs left eye for the first SOA and the controls ($P = 0.008$, one tail *t*-test for comparing a single case with a control group). In contrast, there was no significant difference in performance between her right eye and the controls. To examine the IOR effect, the same comparison was performed for the second and third SOAs. No significant difference was found between the performance of RP and the controls. These data indicate that in the early (first) SOA, RP had no validity effect when her affected left eye was tested but showed such an effect with her normal right eye viewing. The control subjects exhibited a typical validity effect in both eyes.

In endogenous orienting, RP and the control participants demonstrated the typical validity effect, which was not modulated by the viewing eye, and there was no difference in performance between RP and the controls (see Fig. 3 and Supplement 1-b).

4.2. Patient GS

In the exogenous task, a significant difference in GSs validity effect was found between targets in the right and left visual hemifields with left eye viewing at the first SOA ($P = 0.017$, see Supplement 2-a). Specifically, GS showed the typical validity effect and IOR for targets appearing in the right visual field, but no validity effect for targets in the left visual field. This was a result of a slowed response to valid trials in the inaccessible visual field ($P = 0.042$, see Supplement 2-a). GSs right eye showed the typical validity effect and IOR for both visual fields (see Fig. 4). For the control sample, the typical validity effect and IOR were observed and were not modulated by the viewing eye or visual field.

A significant difference was found between the first SOA validity effect of GSs left eye, with the target appearing on the left, to that of the controls ($P = 0.03$, one tail *t*-test for comparing a single case with a control group). No such difference was observed for the second and third SOAs, that is, no difference was observed in

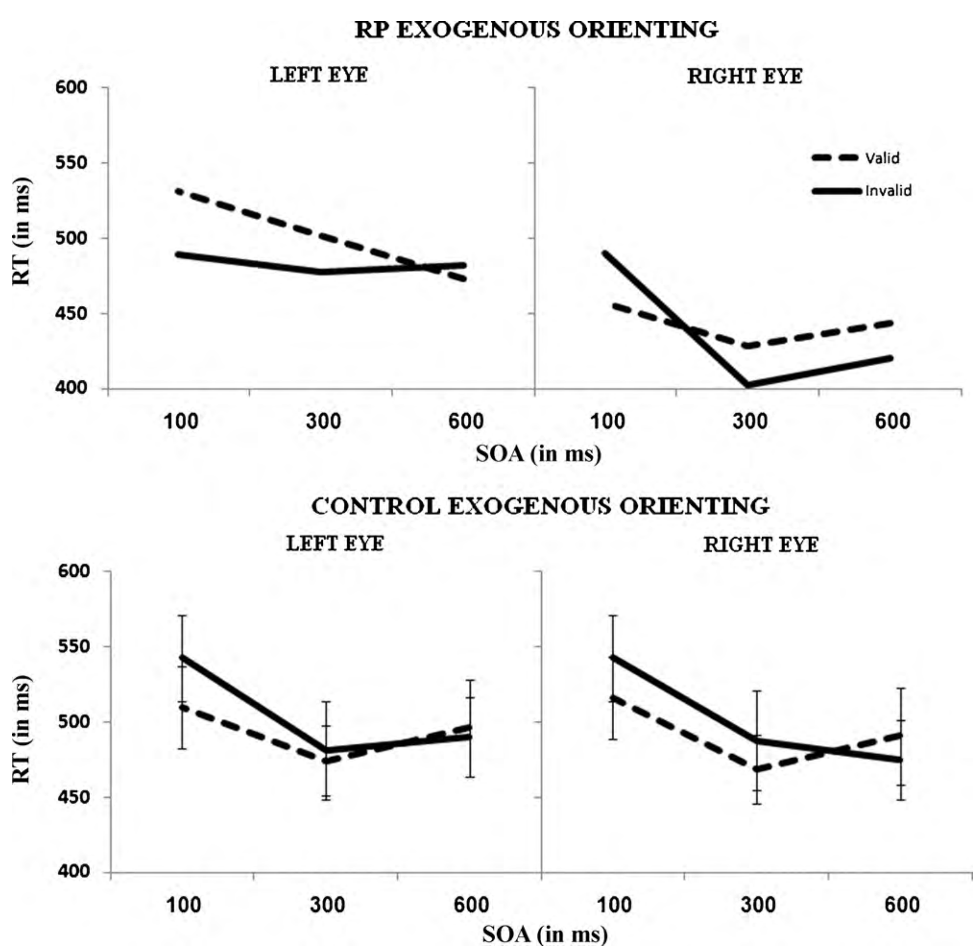

Fig. 2. Reaction time (RT) of exogenous orienting as a function of eye, SOA, and validity for RP and her control group.

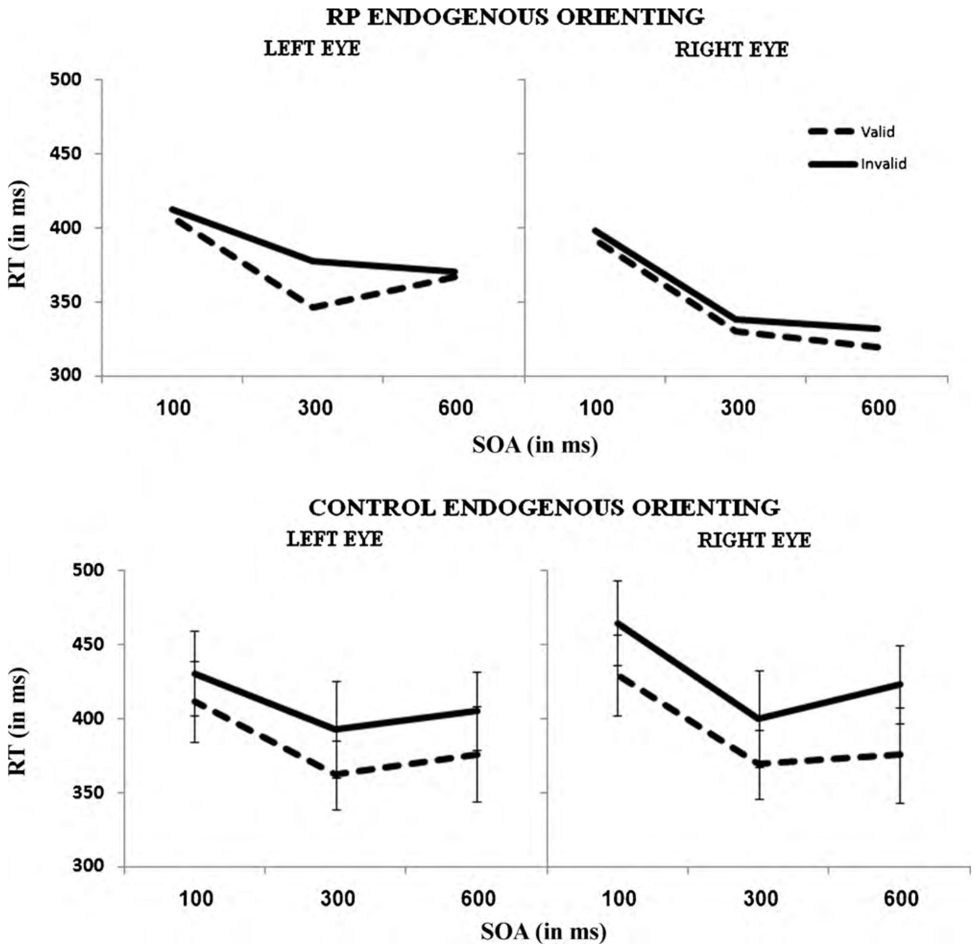

Fig. 3. Reaction time (RT) of endogenous orienting as a function of eye, SOA, and validity for RP and her control group.

the IOR effect. GS also presented a larger validity effect than the controls for the first SOA when viewing with the right eye. These analyses indicate that at the first SOA, GS did not show a validity effect with the affected left eye viewing when the target appeared in the motorically inaccessible left visual field. She exhibited the typical validity effect in all other conditions.

In endogenous orienting, GS and the control participants demonstrated the typical validity effect, which was not modulated by the viewing eye or visual field. GS presented a larger validity for the left eye and left visual field than the controls did (see Fig. 5 and Supplement 2-b).

4.3. Patient SH

For the first two patients we examined exogenous and endogenous orienting while monitoring eye movements using a video camera. Exogenous and endogenous effects are generally found in covert attentional tasks, which do not involve any eye movements. Therefore, deficits in the execution of eye movements cannot explain the lack of the attentional effect. In spite of these considerations, we ran the exogenous task on SH using a video-based desk-mounted eye tracker.

In the exogenous task there was a significant difference in SH's validity effect between the targets presented in the motorically accessible and inaccessible visual fields at the first SOA ($P = 0.05$, see Supplement 3). The validity effect was larger in the accessible than the inaccessible visual fields (see Fig. 6). This was a result of a slowed response to valid trials in the inaccessible visual field ($P = 0.08$, see Supplement 3).

We examined eye movements larger than 2.5° (which is the width of the central box on the display monitor). SH moved her eyes on less than 3% of trials. The paucity of eye movements during performing the task demonstrated that the results could not be explained by the involvement of eye movements.

5. Discussion

Our work presents three patients with Duane Retraction Syndrome, which affects their ocular motor functioning. All three patients were tested with an exogenous cueing task, and two of them were also tested with an endogenous task. As opposed to Craighero et al.'s (2001) results, for the endogenous cueing task, both our patients demonstrated the normal validity effect, regardless of the testing conditions. In contrast, in exogenous cueing, the visual field modulated orienting of attention in all three patients, regardless of the specific eye movement limitation (GS with a uniocular abduction problem, RP with a uniocular abduction and adduction problem and SH with a problem of abduction of both eyes). The pattern of results was uniform for all patients: when targets appeared in a motorically inaccessible visual field, the patients did not show a validity effect, whereas for targets appearing in the accessible visual field, they exhibited the typical validity effect. This result was a product of slowed responses to valid trials at the motorically inaccessible visual fields, which indicates that our patients did not gain from a valid exogenous cue. Attention was not automatically drawn to the exogenous cue when it was presented at a motorically inaccessible location. Both RP and GS demonstrated a reverse validity effect in the inaccessible visual field. This find-

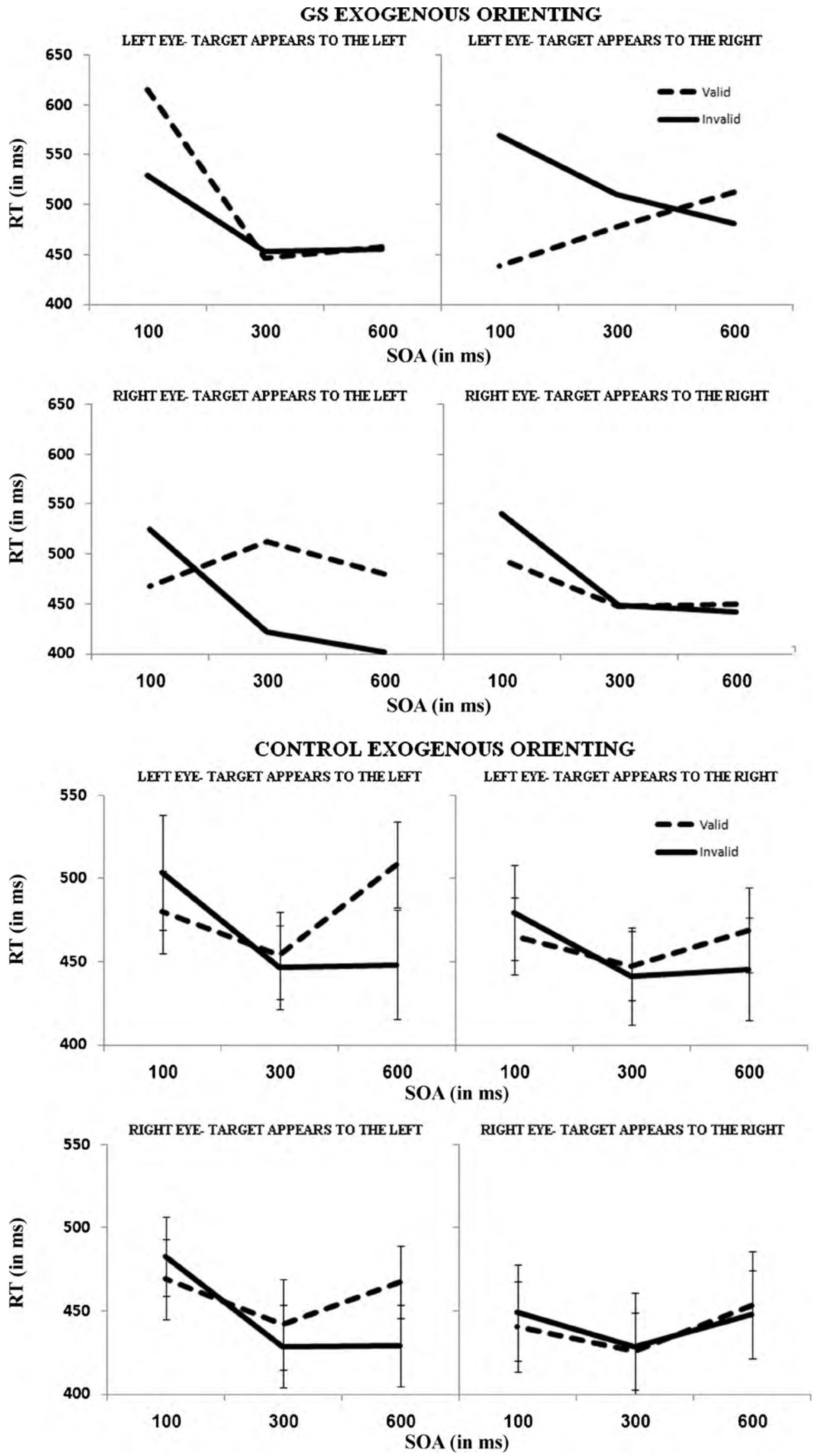

Fig. 4. Reaction time (RT) of exogenous orienting as a function of eye, SOA, visual field and validity for GS and her control group.

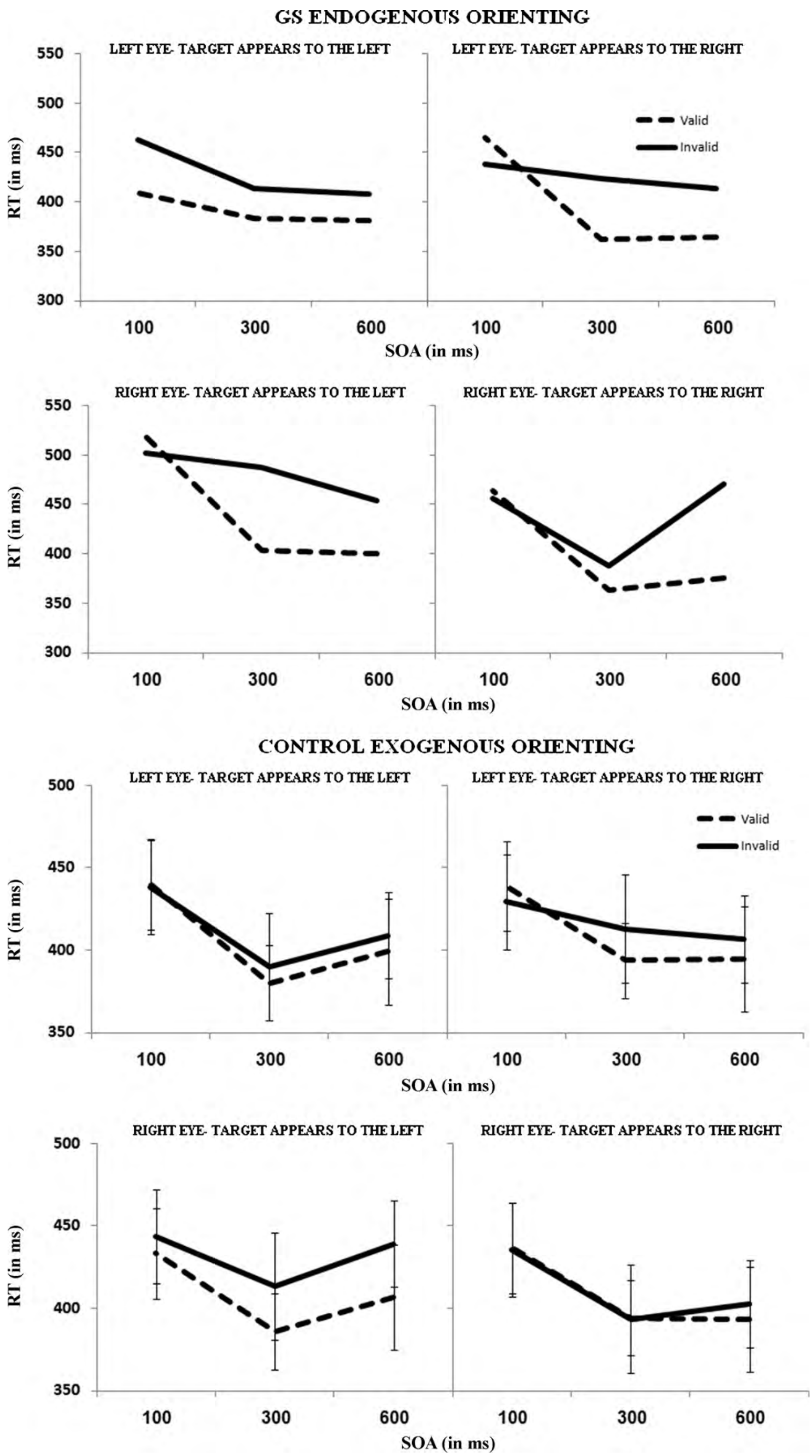

Fig. 5. Reaction time (RT) of endogenous orienting as a function of eye, SOA, visual field and validity for GS and her control group.

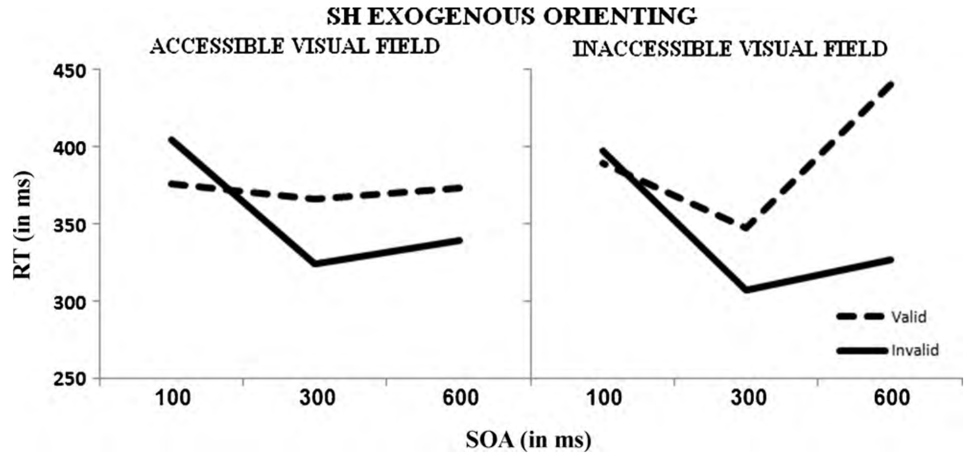

Fig. 6. Reaction time (RT) of exogenous orienting as a function of SOA, accessibility of visual field and validity for SH.

ing might have several explanations. It is possible that with lack of facilitation, IOR is more pronounced and appears earlier. Another possible explanation might be related to the alerting influence of the non-predictive cue. Although a non-predictive cue does not contain spatial information, it does contain temporal information (see Gabay & Henik, 2008). It is possible that the patients' deficit impaired their ability to process the cue (which affected the orienting of attention to it) and also reduced the preparatory component it provides. The reduced preparedness of the patients might have delayed the behavioral response and produced the reversed validity effect. Paucity of eye movements during the testing, confirmed by an infra-red eye movements recording, demonstrated that these results were not confounded by the involvement of eye movements.

Craighero et al. (2001) have demonstrated abnormal orienting of endogenous attention in peripheral sixth nerve palsy patients, but did not examine exogenous attention. In contrast, both the work of Smith et al. (2004), which examined a patient with congenital abnormality of eye movements, and our study demonstrated exogenous but no endogenous deficit. These inconsistent results might originate from differences in patient selection between the studies. The patients of Craighero et al.'s (2001) study suffered from an acquired eye movement deficit, whereas the patients in the other two studies had congenital defects. Moreover, patients in Craighero et al.'s study were tested in the acute stage of the disease (within 15 days after the onset of diplopia), whereas the patients examined in the other two studies had chronic conditions. It is possible that endogenous orienting was normal in our patients because of a compensatory process not yet developed in Craighero et al.'s patients. Another possibility is that endogenous orienting, because of its volitional nature, is more influenced by emotional state. Specifically, if patients are distracted by the fact that they are viewing through their impaired eye, it might influence their performance. Congenital syndromes might be less affected by this disturbance since the patients are used to viewing through their affected eye. An additional difference between the groups of patients is the specific ocular motor pathology. The microvasculopathy causing sixth nerve palsy is a troncular lesion, whereas DRS involves the sixth nerve nucleus as well (see Fig. 7). Another aspect that might impact the allocation of endogenous attention is the presence of diplopia. Sixth nerve palsy patients suffer from diplopia, which is known to influence eye dominance. A suppression of the affected eye (either by an eye patch, a common symptomatic treatment, or self motivated by the patient in order to get a clearer image of the world) might also explain the lack of an endogenous orienting effect. It is noteworthy that the endogenous validity effect was not modulated by ocular motor ability of the affected eye in Craighero et al.'s patients. This result weakens the claim that the abnormal orienting of endogenous attention is a product of motor disability.

Our findings, in accordance with Smith et al. (2004), demonstrate a neuropsychological dissociation between endogenous and exogenous validity effects. Such dissociation has been demonstrated behaviorally by differences in the time course of the validity effect (Shepherd & Muller, 1989) and in brain activations (Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005). This dissociation might indicate a different neural basis for exogenous and endogenous focusing of attention. Only the exogenous orienting requires an operating ocular motor system.

The influence of motor ability on orienting of reflexive attention is most likely embedded in the ability to execute an appropriate eye movement and not in the ability to program the eye movement. In this work all three patients were able to perform eye movements to both visual fields with at least one eye. This means that the central system dealing with programming of eye movement was functioning properly. It is important to note that eye movement programming is not eye specific. As can be seen in Fig. 7, the motor command is first sent to the contra-lateral rectus and then sent to the ipsi-lateral eye by lower motor areas (i.e., through the medial longitudinal fasciculus). Therefore, the fact that our patients were able to perform eye movements to both visual fields in their motorically accessible hemifields suggests that cortical brain areas that are involved in programming eye movements were functioning appropriately. According to the classical view of the premotor theory, our patients should not have presented any attentional deficit. Attention was also directed to a specific location in space and should not have been dependent on the eye that provided the visual information (as both eyes project visual information to both hemispheres according to the visual hemifield). Our patients performed normal orienting of attention to both visual fields in the motorically accessible field. Thus, it is unlikely that the limitation in orienting to the motorically inaccessible field is a result of an undeveloped attentional system, as suggested by Smith et al. (2004). In turn, this implies that appropriate motor functioning (rather than motor programming) is needed for the execution of orienting of attention.

Our findings expand the classical view of the premotor theory (Rizzolatti et al., 1987), which predicts no difference in the attentional ability between patients' eyes. Instead, the results indicate that an ability to perform eye movement is essential in order to allocate reflexive exogenous attention. It seems that feedback from lower motor areas to higher-level structures, which governs orienting of attention, is required in order to orient exogenous attention. Future research should examine whether this feedback is an on-line feedback (i.e., the attentional system receives real time information

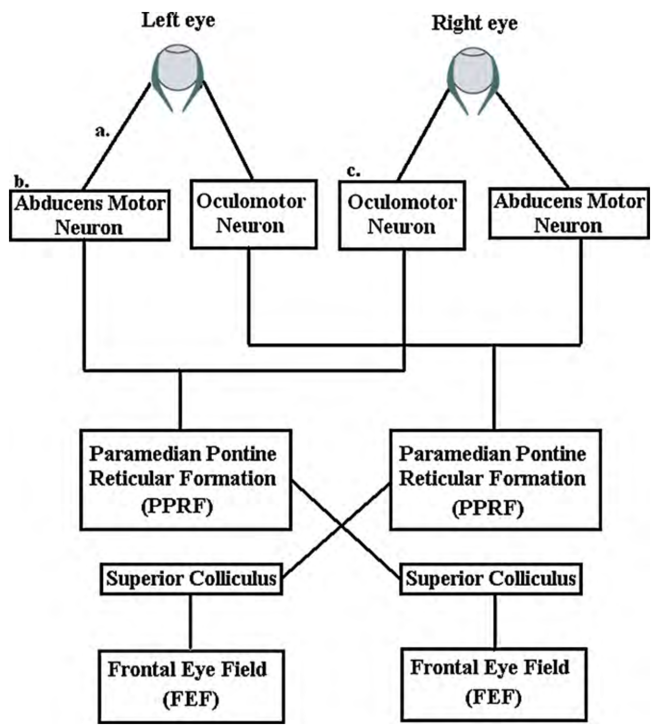

Fig. 7. A simplified flow diagram of the ocular motor anatomy for performing horizontal eye movements. (a) Sixth cranial nerve (the abducens nerve). (b) The abducens motor neuron, which activates the lateral rectus of the left eye. (c) The oculomotor neuron, which activates the medial rectus of the right eye. DRS involves the left cranial nerve and the left abducens motor neuron (indicated by letters a and b). The right eye normal motor ability observed in two DRS patients is an indication that brain areas that are involved in programming of eye movements are intact.

about motor ability) or a long-term feedback (i.e., a developmental influence on the representation of motor ability for a specific eye), and what its exact pathway is.

One locus in which a discrepancy between motor command and actual eye position might be detected is the SC. The SC is involved in programming and execution of eye movements (Sommer & Wurtz, 2002) and in orienting of reflexive attention (Sapir et al., 1999). The SC also contains information about eye position (Campos, Cherian, & Segraves, 2006) that is not a product of downwards proprioceptive information (Guthrie, Porter, & Sparks, 1983). A discrepancy between neural correlates that pass through the SC (Sommer & Wurtz, 2002) and a representation of eye position at the level of the SC might provide information about ocular motor ability to higher brain areas.

Another pathway that might provide such information could be a proprioceptive representation of the eye at the somatosensory cortex. This representation was demonstrated for *Macaca mulatta* (Wang, Zhang, Cohen, & Goldberg, 2007) and humans (Balslev & Miall, 2008). Wang et al. (2007) suggested that this representation might have a more calibratory and perceptual role than a corollary discharge role. A representation of ocular motor disability might be inferred by the lack of activation of the proprioceptive representation of the motorically inaccessible visual field.

In summary, our work demonstrates a link between ocular motor ability and reflexive allocation of attention. We suggest that our patients do not show attentional system deficits, and that the mechanisms underlying programming of eye movements are intact. The influence of motor ability on orienting of reflexive attention is most likely related to the ability to execute an appropriate eye movement and not to the ability to program the eye movement. Attentional orienting in our work was only impaired when targets appeared in the motorically inaccessible visual field. This result indicates a need for some feedback between the attentional system and the ocular motor system for proper orienting of attention. Our patients' deficits likely do not affect brain areas that are involved in programming of eye movements (see Fig. 7) but influence orienting of reflexive attention. In contrast to the classic view of the premotor theory, which predicts a relationship between motor programming and allocation of attention, our work demonstrates a connection between motor performance and allocation of attention.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2010.06.022.

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