Impaired peripheral reaching and on-line corrections in patient DF: optic ataxia with visual form agnosia

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ABSTRACT

An influential model of vision suggests the presence of two visual streams within the brain: a dorsal occipito-parietal stream which mediates action and a ventral occipito-temporal stream which mediates perception. One of the cornerstones of this model is DF, a patient with visual form agnosia following bilateral ventral stream lesions. Despite her inability to identify and distinguish visual stimuli, DF can still use visual information to control her hand actions towards these stimuli. These observations have been widely interpreted as demonstrating a double dissociation from optic ataxia, a condition observed after bilateral dorsal stream damage in which patients are unable to act towards objects that they can recognize. In Experiment 1, we investigated how patient DF performed on the classical diagnostic task for optic ataxia, reaching in central and peripheral vision. We replicated recent findings that DF is remarkably inaccurate when reaching to peripheral targets, but not when reaching in free vision. In addition we present new evidence that her peripheral reaching errors follow the optic ataxia pattern increasing with target eccentricity and being biased towards fixation. In Experiments 2 and 3, for the first time we examined DF's on-line control of reaching using a double-step paradigm in fixation-controlled and free-vision versions of the task. DF was impaired when performing fast on-line corrections on all conditions tested, similarly to optic ataxia patients. Our findings question the long-standing assumption that DF's dorsal visual stream is functionally intact and that her on-line visuomotor control is spared. In contrast, in addition to visual form agnosia, DF also has visuomotor symptoms of optic ataxia which are most likely explained by bilateral damage to the superior parietal occipital cortex. We thus conclude that DF can no longer be considered as an appropriate participant for testing the neural basis of perception and action.

KEYWORDS

Perception-action model; dorsal visual stream; on-line corrections; patient DF; SPOC

1. Introduction

According to the influential perception-action model (Goodale & Milner, 1992; Milner & Goodale, 1995, 2006) the two cortical streams of visual processing are specialised for distinct behavioural functions: the dorsal (occipito-parietal) stream supports the visual control of actions, and the ventral (occipito-temporal) stream mediates vision for perception. Over the last 25 years this model has received strong support from monkey neurophysiology, neuroimaging and behavioural experiments in neurologically intact participants (Milner & Goodale, 2008; Goodale, 2011, 2014); but the most widely influential evidence for its key assertions comes from reported perception and action dissociations in neurological patients (Milner et al., 1991; Goodale et al., 1991; Goodale & Milner, 1992).

DF is an extensively-studied patient who acquired profound visual form agnosia following bilateral ventral stream damage sustained in a near-fatal episode of carbon monoxide poisoning (Milner et al., 1991). Despite her inability to identify and distinguish visual stimuli, DF could still use visual information to control her hand actions towards these stimuli (Milner et al., 1991; Goodale et al., 1991; Goodale et al., 1994). While her perceptual deficits were directly linked to extensive bilateral damage to her ventral stream, her spared visuomotor skills were attributed to an intact dorsal stream (Milner et al., 1991; Goodale et al., 1991; Goodale et al., 1994; James et al., 2003). Consistent with this picture, a complementary dissociation was claimed for patients with dorsal stream lesions and optic ataxia, who were impaired in action but had intact perceptual abilities (Rossetti, Pisella & Vighetto, 2003; Rossetti et al., 2005; Perenin & Vighetto, 1988; Karnath & Perenin, 2005). These contrasting patterns have been widely interpreted as a double dissociation between visual form agnosia (DF) and optic ataxia (e.g., Goodale & Milner, 1992; Milner & Goodale, 1995, 2006; Rossetti, 1998).

However, in recent years, the evidential basis for this double dissociation has been questioned. Firstly, it has been pointed out that the behavioural evidence for a double-dissociation is, at best incomplete, since the two patient groups (visual form agnosia and optic ataxia) have not been tested under appropriately matched conditions (Rossetti, Pisella & Vighetto, 2003; Pisella et al., 2006). Pisella and colleagues (2006) emphasised that the visuomotor deficits in optic ataxia are generally restricted to peripheral vision, with performance near-normal in central vision; however, the sparing of perceptual functions in these patients had been shown mainly in central vision. Where more specific assessments of perception in peripheral vision had been made, there was mounting evidence for significant deficiencies in optic ataxic patients (Michel & Henaff, 2004; Perenin & Vighetto, 1988; Pisella et al., 2009; Rossetti et al., 2005). These perceptual deficiencies are now widely accepted, though it is still unclear whether they are secondary to problems orienting attention toward the affected region of space (Blangero et al., 2010; McIntosh et al., 2011; Michel & Henaff, 2004; Pisella et al., 2009; Striemer et al., 2007, 2009).

In visual form agnosia (represented chiefly by patient DF), the common contrast has been done between impaired perception and preserved action in central vision. In fact, the evidence on DF's visuomotor guidance to peripheral visual targets is limited to one brief report within a book chapter (Milner, Dijkerman & Carey, 1999), describing a task that "*required DF to make manual pointing responses towards targets presented at eight different locations… in the frontal plane of the subject*" (p.447). Target locations were not further specified, and the report did not state whether and how fixation was controlled, nor for how long were the LED targets lit. Data analysis was via a graphical comparison of DF's mean absolute error (across all locations) to three control subjects. This experiment has not been formally reported, although the data figure has been reproduced at least twice (Figure 14.4, Carey, 2010; Figure 2, Milner & Goodale, 2008). So although the figure did not suggest any

problem with immediate pointing to peripheral targets (albeit DF's mean error is marginally higher than in controls), the issue clearly merited further study, especially given the theoretical importance of the proposed double-dissociation with optic-ataxia.

To fill this gap, Hesse, Ball & Schenk (2012, 2014) investigated DF's performance in central and peripheral vision in more detail, studying grip-scaling in grasping and accuracy in pointing. Surprisingly, rather than showing the expected preservation across the visual field, DF's pattern matched that found in optic ataxia, with good performance when free vision was allowed, but impaired grip-scaling and pointing accuracy for peripheral targets when fixation was controlled. Although not formally analysed, the general character of the impairment was also similar to optic ataxia, in that the grasp tended to be uniformly over-scaled, and pointing in either hemifield erred toward fixation, increasing in magnitude with target eccentricity (across the two studies, targets from 4° to 18.4° were tested). The second of these studies showed that DF's pointing impairment affected both hands, as well as both visual fields (Hesse et al., 2014).

Hesse and colleagues entertained two main possibilities to explain these unexpected facts. The first is that visuomotor deficits resembling optic ataxia can arise from the ventral stream damage that has been emphasised in case descriptions of DF. The second is that the resemblance is not coincidental, and that DF actually has optic ataxia, in addition to visual form agnosia, due to damage to her dorsal stream bilaterally. This second account would be consistent with the typically diffuse consequences of carbon monoxide intoxication, and gains considerable plausibility from a close reading of the brain imaging findings in DF. Milner et al. (1991) indeed noted, at one year post-accident, bilateral damage in DF's medial parieto-occipital cortex, though James et al's well-cited fMRI study (2003) reported only a small lesion in the left posterior parietal cortex (see also Steeves et al., 2006 and Cavina-Pratesi et al., 2010a,b). The most recent MRI study has confirmed that DF's cortical thickness

is considerably reduced in both left and right intraparietal and parieto-occipital sulci (Bridge et al., 2013).

In James et al's functional data, the only dorsal stream region robustly and specifically active during grasping, compared with reaching, with the dominant (right) hand was the right anterior intraparietal sulcus (aIPS). This is consistent with a key role for aIPS in grasping in both humans and monkeys (Binkofski et al., 1998; Culham et al., 2003; Frey et al., 2005; Begliomini et al., 2007a,b; Cavina-Pratesi et al., 2010c; Monaco et al., 2014, 2015; Murata et al., 2000; Gardner et al., 2007; Davare et al., 2007). James et al. (2003) thus concluded that DF's dorsal stream was functioning well, explaining her spared visuomotor skills. Nevertheless, DF's right-lateralized activation contrasts with the usual left-dominant activation for right hand grasping reported in healthy participants (Beurze et al., 2007; Stark & Zohary, 2008; Gallivan et al., 2013; Rossit et al., 2013). Moreover, unlike controls, DF showed no significant activation, during reaching or grasping, in either left or right superior parieto-occipital cortex (SPOC) (James et al., 2003). SPOC has repeatedly been shown to be involved in visuomotor control in humans and monkeys (Astafiev et al., 2003; Connolly, Andersen & Goodale, 2003; Prado et al., 2005; Filimon et al., 2009; Cavina-Pratesi et al., 2010c; Gallivan et al., 2011; Monaco et al., 2011, 2015; Rossit et al., 2013; Martin et al., 2015; Fattori et al., 2001; 2009, 2010; Breveglieri et al., 2016), and damage to this region provokes visuomotor deficits including peripheral misreaching, the core sign of optic ataxia (Battaglini et al., 2002; Karnath & Perenin, 2005; Pisella et al., 2009; Rossit et al., 2009; Hwang et al., 2012; Anderson et al., 2014).

The idea of bilateral damage to the parieto-occipital cortex, with functional impairment of SPOC bilaterally (and, perhaps, aIPS in the left hemisphere) could very well explain why Hesse and colleagues (2012, 2014) found DF to show classic signs of optic ataxia. It is less clear why Hesse and colleagues' data were so starkly at odds with the prior

report of accurate peripheral pointing in DF (Milner, Dijkerman & Carey, 1999); but the brevity of that prior report of peripheral pointing precludes any meaningful comparison of the two datasets. Whitwell, Milner and Goodale (2014) recently suggested that DF's dorsal stream atrophy, and by implication her visuomotor impairment, may have increased since the first scans, but this remains to be confirmed.

Regardless of whether DF's dorsal stream lesions have progressed over time, it has been noted that her visuomotor performance is not entirely normal, even in free vision, and even in the original experimental reports (Goodale et al., 1991; Milner et al., 1991; Goodale, Meenan et al., 1994). These classic reports were based on clear qualitative contrasts between DF and healthy controls, but statistical methods for finer-grained single-case analyses have since been developed (Crawford & Garthwaite, 2005, 2006; see McIntosh & Brooks, 2011, for an overview). Himmelbach, Boehme and Karnath (2012) applied these newer methods to the archived data from some of DF's seminal studies, testing a larger sample of control subjects (n=20) on the original tasks used. They found that DF's grip scaling for rectangular objects was within normal limits, but that she had significant visuomotor deficits when grasping irregular shapes, or posting a card through an oriented slot. Her visuomotor performance was still *differentially* preserved, relative to her performance on perceptual tasks. This re-analysis recasts the seminal observations of patient DF as showing a strong, rather than a classical, dissociation between perception and action in central vision (Crawford, Garthwaite, & Gray, 2003; see also Whitwell, Milner & Goodale, 2014).

It is also now well-recognised that DF encounters problems in a variety of complex visuomotor tasks, and that her control of even rudimentary actions may be supported by impoverished visual information (see Schenk & McIntosh, 2010, for a review). Schenk and McIntosh interpreted these patterns as evidence of an intimate ventral stream involvement in action, with the relative preservation of DF's basic visuomotor skills attesting to an

impressive robustness of the system in adapting to the loss of this contribution (see also Schenk, 2010). However, in light of recent data, it now seems possible that at least some of her visuomotor abnormalities in central vision may be directly due to dorsal stream damage.

Re-inspection of kinematic data from DF, in a variety of reaching and grasping tasks reveals that, even when she performs a task well, she tends to be slow, with low peak velocities, and movement times up to twice as long as those of controls (Carey, Dijkerman & Milner, 2009; Dijkerman et al., 2009; Hesse et al., 2012; Dijkerman, Milner & Carey, 1996; Goodale et al., 1994; Marotta, Behrmann & Goodale, 1997; McIntosh et al., 2004; Mon-Williams, McIntosh & Milner, 2001; Rice et al., 2006; Milner, Dijkerman & Carey, 1999). Rice et al. (2006) reported that patients DF and SB (another visual form agnosic patient with large bilateral lesions) moved much more slowly than controls in a perceptually-guided task, but that DF (not SB) was also slow in the direct reaching task. This suggests that DF's slowing is not a generalised effect of brain damage, but may be a more specific consequence of, or compensation for, damage to the visuomotor network. In this respect, she is also similar to patients with optic ataxia, in whom relatively good visuomotor guidance in central vision is nonetheless associated with slowed execution (Gréa et al., 2002; Rice et al., 2008; Schindler et al., 2004).

A remarkable picture is thus building in which patient DF, the epitome of ventral stream perceptual problems, may also have optic ataxia, the cardinal dorsal stream disorder. Hesse and colleagues (2012, 2014) have so far shown that she misreaches and shows impaired grip-scaling in peripheral vision, with much better performance in central vision. In this paper, we confirm this pattern of peripheral misreaching, presenting data that predates Hesse and colleagues' tests, and show that peripheral misreaching was already present in 2010. We provide a novel analysis of directional (rather than absolute) pointing errors, to test whether DF's misreaching is significantly biased towards fixation as reported for optic ataxia

(Blangero et al., 2010; Milner et al., 1999, 2003; Rossetti et al., 2005). We then present data on the on-line correction of reaching, proposed by some as the most specific function of dorsal stream control (Pisella et al., 2000; Glover, 2003; Schenk & McIntosh, 2010), classically impaired in optic ataxia (Blangero et al., 2010; Gréa et al., 2002; McIntosh et al., 2011; Pisella et al., 2000). In fixation-controlled and free-vision versions of the task, we show dramatic deficits of on-line control in patient DF, comparable to those seen in optic ataxia. We thus provide further evidence for the idea that DF has bilateral optic ataxia alongside visual form agnosia. We discuss the implications of this conclusion for the proposed double dissociation between these conditions, for the perception-action model, and for the status of patient DF as an experimental subject.

2. Experiment 1: Reaching to stationary targets in free vs. peripheral vision

2.1. Methods

2.1.1 Participants

Patient DF: A right-handed female 56-year-old patient (DF), who after carbon monoxide poisoning in 1988 acquired visual form agnosia (Milner et al., 1991), participated in the experiment (tested at the University of Glasgow in 2010). Previous testing (Milner et al., 1991; Humphrey et al., 1994) demonstrated that DF is severely impaired in visual shape, orientation and distance discriminations leading to poor visual object recognition, but shows preserved colour, luminance and texture perception (Milner et al., 1991; Milner & Goodale, 1995; 2006). MRI scans of patient DF revealed large bilateral lesions in the lateral occipital-cortex, but leaving V1 and fusiform gyrus largely intact, and a small lesion in the left posterior parietal cortex (James et al., 2003; but see introduction for a fuller discussion of dorsal stream involvement). An in-house computerized static perimetry test (up to 22º of eccentricity; Rossit et al., 2009) revealed that DF was able to detect visual stimuli above

chance in the upper visual field, but similarly to previous studies (e.g. Hesse, Ball & Schenk, 2012, 2014; Bridge et al., 2013) showed a lower right quadrantanopia when tested below 11º of visual eccentricity. This finding is also consistent with the report of a lesion to the anterior portion of V1 in the left hemisphere (Milner et al., 1991; Bridge et al., 2013)

Control group: Six age-matched right-handed healthy control participants (mean age: 53.5 years, SD 8.3; age range: 45-63 years; 2 females) were tested. All participants had normal or corrected-to-normal visual acuity and no history of neurological problems. All experiments were approved by the local ethical committee and all participants (including patient DF) gave informed consent prior to the study.

2.1.2. Apparatus and stimuli

Targets and fixation were 7mm circles (0.7º of visual angle) back-projected (HITACHI CP-X345 Multimedia LCD projector, refresh rate of 60Hz) onto a horizontal Perspex box (77cm width/97cm length/30cm height) via a reflection mirror (3mm thick, 60cm x 60cm). The box was placed on top of a wooden table at which the subjects were seated. The targets were red and presented at -20º, -15º, -10º, 0º, 10º, 15º and 20º of visual eccentricity. The fixation circle was green and placed 2.6º above the central target location (allowing all targets to be presented outside of DF's scotoma). The room was slightly darkened so that the targets were clearly visible, but the participant's hands were visible throughout the movement.

Pointing responses were recorded by sampling the 3D position of a magnetic marker, attached to the tip of the right index finger, at a rate of 108Hz, using an electro-magnetic motion-analysis system (Minibird, Ascension Technology Inc.). Experiments were programmed in LabVIEW (National Instruments). The electrooculogram (EOG) was continuously recorded from electrodes placed above and below the left eye (vertical EOG) and from electrodes placed on the left and right outer canthi (horizontal EOG) using a BIOSEMI Active-Two amplifier system. Two additional electrodes (Common Mode Sense

[CMS] active electrodes and Driven Right Leg [Driven Right Leg] were place within a standard BioSemi head cap [see www.biosemi/faq/cms&drl.htm for details]). The data were recorded at 2048 Hz.

2.1.3. Procedure

Participants sat in an adjustable chair and began each trial with their right index-finger resting on a start button located approximately 35 cm from the middle target and aligned with their sagittal midline. Two reaching conditions (separate blocks of periphery and free vision) were completed using the right index-finger. Block order was the same across participants so that controls performed the experiment in the same order as DF. In the first block, participants were asked to point to the target whilst maintaining fixation on the central light (peripheral vision). In the second block, participants were asked to point to the target but were allowed to move their eyes (free vision). Target onset was triggered by start button press and the target remained visible until the end of the trial. The green fixation circle was displayed continuously throughout the experiment. Each target was presented 6 times, in randomly-shuffled order, resulting in a total of 42 trials per block (plus 5 practice trials). At the end of these tasks, calibration coordinates were obtained by continuous presentation of each target position, one by one, allowing the participants to adjust their terminal fingertip position until they felt that they had perfectly occluded the target. There were 3 calibration trials for each target and start position.

After the reaching tasks, participants performed a perceptual target detection task (in peripheral vision only) using the same set-up. Each of the targets was presented 10 times, in randomly-shuffled order, and participants were asked to press the button upon target detection whist maintaining fixation. To control for response biases, 20 catch trials in which no target appeared were randomly intermingled.

2.1.4. Data analysis

The EOG data were analysed using BESA (www.besa.de) and custom MATLAB scripts. The continuous data were band-pass filtered (0.01 Hz - 40 Hz). The EOG epoch started 200 ms before trial onset and lasted 2200 ms. The 200 ms prior to trial onset served as the baseline. Visual inspection of the epoched EOG data demonstrated target-related horizontal EOG activity in the free movement condition that was related to target location for the control subjects. For the fixation condition both controls and patient DF showed greatly reduced horizontal EOG activity. Thus, we are confident that participants were able to follow task instructions. Individual trials with clear target related horizontal EOG activity between trial onset and response execution within the fixation condition, were visually identified and removed from the subsequent movement data analysis. This resulted in the removal of 2% of trials for controls whereas no trials were removed for patient DF, as she was able to maintain fixation throughout. The remaining reaching data were filtered by a dual-pass through a second-order Butterworth filter with a cut-off frequency of 10 Hz, and analysed using customized software written in LabVIEW (National Instruments). For the reaching task we computed directional error (signed angular deviation of the movement endpoint relative to the ideal reach), and for the detection task the percentage correct and reaction time (RT).

DF's performance was compared to that of the controls using modified t-tests developed for single-case studies (Crawford & Garthwaite, 2002). The revised standardized difference test (RSDT; Crawford & Garthwaite, 2005) was used to compare between-task differences in DF and controls. One-tailed tests were used for tests in which there was an unambiguous directional prediction, but not where impaired performance could differ in either direction from controls.

2.2. Results

In free vision, the reaches of patient DF had similar end-point coordinates to the ones of control participants (Fig. 1). Modified t-tests on directional error (Fig. 2) found no abnormality in DF at any target position (all two-tailed *ps* > 0.1).

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Figure 1 about here

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However, DF was severely impaired when reaching to targets in peripheral vision. There was less differentiation of target eccentricity in DF than in controls (Fig.1); she presented a bias towards the midline/fixation (Fig.1); she undershot target position (especially when reaching to rightward targets; Fig.1); and her errors increased dramatically with target eccentricity (Fig.2). Modified t-tests on directional error confirmed that, when compared to controls DF significantly undershot target positions (i.e., had a bias towards fixation) in the right visual field (20°: t = -11.3, two-tailed $p < 0.001$; 15°: t = -10.4, two-tailed $p < 0.001$; 10°: t = 5.3, two-tailed $p = 0.003$) and for the -20° and -15° targets in the left visual field (-20: t = 3.8, two-tailed $p = 0.01$; -15°: t = 2.9, two-tailed $p = 0.03$), though not for the -10° left target (t = 2.2, two-tailed $p = 0.08$). Her errors for the central (0°) target were well within normal limits (t = 0.5, two-tailed $p = 0.61$).

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Figure 2 about here

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To test the apparent dissociation between free vision and peripheral reaching, we applied the RSDT, using directional error averaged over all target positions, but excluding the 0° target. This confirmed that the difference in accuracy between free and peripheral reaching was significantly larger in DF than in controls fulfilling the criteria for a classical dissociation (mean difference DF = 3.6°; mean difference controls = 0.1°; t = 5.2, two-tailed $p = 0.003$).

To investigate perceptual detection of targets in our stimulus set-up we tested DF and controls in an additional perceptual target detection task. The controls were at ceiling, being able to detect all targets (100% correct in both target present and target absent trials). Patient DF's performance was also very good with 100% correct in target absent trials (i.e., no false positives) and when targets ware presented at -15°, -10°, 15° and 20° of eccentricity. For -20°, 0° and 10° targets her performance was 90% correct (i.e. she missed one trial per target eccentricity). However, DF took significantly longer to detected all target positions when compared to controls (-20°: t = 105.3, one-tailed $p < 0.0001$; -15°: t = 27.4, one-tailed $p < 0.0001$; -10°: t = 6.2, one-tailed $p = 0.0008$; 0°: t = 39.1, one-tailed $p < 0.0001$; 10°: t = 6.5, one-tailed $p = 0.0006$; 15°: t = 3.8 , one-tailed $p = 0.0006$; 20°: t = 2.2, one-tailed $p = 0.04$; see Fig.2C). Nevertheless there was no obvious relationship between her ability to point to or perceptually detect targets in peripheral vision. In particular, and as can been seen by contrasting Figs.2B and 2C, while her pointing errors increased with target eccentricity, her RT did not (if anything, it seemed to decrease) and while she was perfectly accurate in pointing to the central (0°) target, she was significantly slow to detect it.

2.3. Discussion

In Experiment 1, we investigated how patient DF performed on the typical diagnostic task for optic ataxia of reaching in central and peripheral vision. Consistent with the reports of Hesse, Ball and Schenk (2012, 2014), she performed very well with free vision, but was dramatically

impaired for peripheral targets. The difference between her central and peripheral reaching errors met formal criteria for a classical dissociation. We thus replicate the key finding of Hesse, Ball & Schenk (2012, 2014), that DF exhibits the core diagnostic symptom of optic ataxia (Perenin & Vighetto, 1988). In addition we show that her errors follow the pattern typical of optic ataxia, being significantly deviated towards fixation, and increasing with target eccentricity (Blangero et al., 2010; Perenin & Vighetto, 1988; Milner et al., 1999; 2003; Rossetti et al., 2005). Misreaching was present in both visual fields (if anything, more severely on the right), consistent with bilateral thinning of the parieto-occipital cortex (Bridge et al., 2013), the cardinal area associated with this symptom (Karnath & Perenin, 2005). Our test session preceded that of Hesse, Ball & Schenk (2012), so we can confirm that this visuomotor impairment was already present in 2010. It may possibly have been present, but undetected, much earlier, given the mention of bilateral parieto-occipital lesions in a very early case report of patient DF (Milner et al., 1991).

DF was also impaired in our target detection task, showing abnormally slow RTs for all locations but one (the rightmost), which is hard to interpret. On the one hand, DF has profound perceptual problems, which might make the pattern unremarkable, although agnosic patients should be able to perform detection well. On the other hand, patients with optic ataxia also have deficits in detecting visual targets, especially in their ataxic field (Striemer et al., 2007, 2009; Pisella et al., 2007). As found for DF, slowed detection may not modulate with eccentricity in the same way as reaching errors do (Striemer et al., 2009). It is thus conceivable that DF's slowed *perceptual* detection also depends more on her dorsal than ventral stream damage.

Misreaching to peripheral visual targets is the classic diagnostic sign of optic ataxia, but another common feature of the condition – when it has been tested – is an impaired ability to quickly correct reaching movements on-line (Blangero et al., 2010; Gréa et al.,

2002; McIntosh et al., 2011; Pisella et al., 2000). This has typically been studied via 'double-step' reaching tasks, in which the target is displaced abruptly to a new location once the reach is underway. Healthy participants update their movement rapidly to track the displacement, reaccelerating within ~110 ms, and taking a distinguishable spatial path by about 200 ms (Brenner & Smeets 1997; Castiello, Paulignan & Jeannerod, 1991). This response is automatic, occurring without instruction (Day & Lyon, 2000; Pisella et al., 2000), without tapping cognitive resources (McIntosh, Mulroue & Brockmole, 2010), and without any necessary awareness of the target jump or the compensatory correction (Goodale, Pelisson & Prablanc, 1986; Pelisson et al. 1986). The fast automatic corrections depend on dorsal stream integrity, and are impaired in optic ataxia (although slower, conscious corrections may still be made; Pisella et al., 2000; Gréa et al., 2002; Blangero et al., 2010; McIntosh et al., 2011). Thus, in Experiment 2, we examined DF's on-line corrections in a double-step reaching task, with controlled fixation, previously used for the single-case study of a patient (IG) with bilateral optic ataxia (McIntosh et al., 2011).

3. Experiment 2: On-line reaching correction, with fixation controlled

3.1. Methods

The methods used for DF differed in one major design aspect from the ones used in McIntosh et al. (2011), having a reduced number of experimental conditions to focus on the question of interest, and in some more superficial details of apparatus used, as the original experiment, conducted at the University of Lyon, had to be recreated at the University of Edinburgh[1]. The

[1] The apparatus used for DF differed from that used in the experiment of McIntosh et al (2011) in the following respects: stimuli were controlled via LabVIEW rather than Cambridge Research Systems Visual Stimulus Generator; stimuli were presented on a 17" LCD flatscreen, rather than a 21" CRT monitor (stimulus dimensions were unchanged);

methods reported here apply to the testing of patient DF, with methodological differences from the original study noted. The control data come from the original study reported by McIntosh et al (2011), as the methods were closely comparable.

3.1.1. Participants

Patient DF who suffers from visual form agnosia (see section 2.1.1 for details) performed this experiment in 2008 (she was 54 years old at the time).

Control group: Eleven right-handed healthy controls were also tested (mean age: 35.1, SD 9.2; age range: 25–52 years; 8 females). Because DF was at the upper end of the control range of ages, age was used as a covariate in comparing DF's performance to that of controls (see *3.1.4. Data Analysis*). All control participants had normal or corrected to normal visual acuity with no history of neurological conditions. All methods were approved by the relevant local ethical committee and all participants (including patient DF) gave informed verbal consent prior to the study.

3.1.2. Apparatus and stimuli

DF sat in darkness, 420 mm in front of a 17″ CRT monitor (refresh rate 60 Hz), with her head immobilised in a chin-rest. Throughout each trial, she fixated a 6 mm (0.8° visual angle) grey cross, at the screen centre. Targets were 12.5 mm diameter (1.7° visual angle) white circles which appeared either centrally or 65 mm (8.8° visual angle – just outside of paracentral vision in near peripheral vision) to the left or right. Reaching responses were recorded via an Optotrack Certus system (Northern Digital Inc.), which sampled the 3D position of an infrared emitting diode, attached to the nail of the right index finger, at 200 Hz. In the

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EOG, rather than a video-based eye-tracker, was used to monitor fixation; an Optotrak Certus rather than Optotrak 3020 system was used for hand movement recording; and a simple finger tap rather than a button press was used to respond in the perceptual discrimination task.

perceptual task, an infrared emitting diode was attached to both the left and the right index fingernail, with finger position sampled at 200 Hz. Throughout all trials in both tasks, horizontal eye movements were monitored using EOG, with a passive electrode placed on the outer canthus of each eye, and a reference electrode on the forehead. EOG voltage was sampled at 500 Hz, with sampling time-locked to hand movement recording via the Optotrak Data Acquisition Unit (ODAU).

3.1.3. Procedure[2]

DF performed two tasks, reaching and perceptual discrimination, with reaching first. Prior to each task, a 20 second EOG calibration recording was made in which DF was required to follow a fixation cross, which jumped sequentially, approximately every 1-2 seconds between the three target positions.

In the reaching task, DF pressed a button in front of her, with her right index finger, and target 1 appeared at the screen centre. She was then required, in her own time, to initiate a fast forward-and-upward reach towards it (straight line distance 500 mm). Button release triggered the replacement of target 1 by target 2, which was identical to target 1, and either located centrally (static trials) or 65 mm to the left or right (jump trials). A pacing beep, 450 ms after button release, encouraged DF to make fast movements, as she was instructed to try

[2] McIntosh et al (2011) conducted the reaching and perceptual tasks under three different blocked fixation conditions, in order to investigate some specific aspects of visual responsiveness in optic ataxia. Because these extended questions were of less relevance to DF, the present experiment used the central fixation blocks only. DF performed three blocks of the reaching task with central fixation, whereas controls performed two blocks in each of three fixation conditions. DF performed two blocks of the perceptual discrimination task with central fixation, whereas controls performed two blocks in each of three fixation conditions.

to complete the movement by the time of the beep. DF performed three blocks of 60 trials (40 static, 10 jump left, 10 jump right, pseudo-randomly ordered).

The perceptual discrimination task used the same set-up, except that DF's right and left index fingers were raised slightly above the table-top in front of her. The experimenter initiated onset of target 1, which was replaced by target 2 after 500 ms. DF discriminated the direction of the target jumps by tapping the table with the corresponding finger as soon as possible, withholding responses on static trials. Trials timed out after 2000 ms. There were two blocks of 45 trials (15 static, 15 jump left, 15 jump right, pseudo-randomly ordered).

3.1.4. Data analysis

For monitoring of eye position, the raw EOG voltage data were filtered by a dual-pass through a second-order Butterworth filter with a cut-off frequency of 10Hz. The velocity of the EOG signal was computed for each sample. A threshold for saccade identification was determined manually from the calibration recording, as the smallest velocity value that cleanly separated saccades between target locations from inter-saccadic EOG velocity variation. In experimental trials, central fixation was deemed to have been broken on any trial in which the velocity exceeded this threshold value, with saccade onset time corresponding to the frame that the threshold was first exceeded. Fourteen trials (11 static and three jump trials) were removed for the reaching task, because a saccade was initiated before the end of the reach; eleven of these were in the first block, indicating that DF gained better control over her fixation as the task progressed. Five additional trials were lost to recording errors. The loss of 19 trials overall for DF was more than offset by the fact that she performed an extra block of trials (relative to controls), leaving 105 static, 29 jump left and 28 jump right trials for analysis. In the perceptual task, no saccades were detected that preceded the manual response, so no trials were removed.

Kinematic data from reaching movements were filtered by a dual pass through a Butterworth filter with a cut-off of 10 Hz. Movement onset was determined using a velocity threshold of 100 mm s^{-1}, and movement offset using a threshold of 50 mm s^{-1}. The analysis of the spatial trajectory was performed by projecting the hand path onto the plane intersecting the start button and the three target locations, with its origin at the start button. A straight path from start button to the central target defined increasing depth displacement. Leftward lateral displacement was signed negatively, and rightward positively.

The analysis of on-line corrections in individual jump trials was based upon deviations of the hand path from the average spatial path of the hand on static trials, using a bandwidth based upon the movement variability of control participants. First, the spatial trajectories for all static trials were normalised to 1 mm increments along the depth axis. Second, for each participant, the average lateral coordinate and its standard deviation were calculated at each depth increment. Third, the average standard deviation was calculated across all control participants at each depth increment, and these were used to define standard cut-offs for all participants, including DF, for the purposes of classifying corrections in jump trials. Standard cut-offs were used so that the sensitivity of the analysis of corrections would be minimally influenced by individual differences in movement variability. At each depth increment, cut-offs were set at 2.81 average standard deviations either side of that participant's average hand path. For each jump trial, in each time frame, the movement was classed as corrected if it fell beyond the corresponding cut-off in the direction of the jump, being otherwise classed as uncorrected. Each comparison thus approximates a one-tailed comparison at alpha ~ 0.0025, matching that applied by McIntosh et al (2011). The comparison made for the final frame of the movement defined the terminal correction status for each jump trial.

For the reaching task we extracted correction time (for corrected trials only) and directional error for all trial types and compiled a temporal profile of current percentage of corrections for left and right target shifts. For the perceptual task, percentage correct and RT were computed for left and right jumps. DF's performance was compared to that of the controls, with age-entered as a covariate, using Bayesian tests for deficit in the presence of covariates (Crawford, Garthwaite and Ryan, 2011). One-tailed tests were used for tests in which there was an unambiguous directional prediction, but not where impaired performance could differ in either direction from controls.

3.2. Results

DF presented a similar number of terminal corrections to controls with 79% of movements corrected to left jumps and 82% to right target jumps (left jumps: control mean = 86%, SD = 35%; right jumps: control mean = 92%, SD = 28%). However, her movement time was almost double that of controls for static trials (DF = 809.7; controls mean = 462.7, SD = 70.4; Bayesian one-tailed $p = 0.0005$, Z-CCC = 6.29), for left jumps (DF = 862.8; controls mean = 502.3, SD = 71.3; Bayesian one-tailed $p = 0.0004$, Z-CCC = 6.38), and for right jumps (DF = 733.2; controls mean = 443.7, SD = 66.3; Bayesian one-tailed $p = 0.001$, Z-CCC = 5.48). In fact, during data collection we kept reminding DF to move faster, but this was the maximum speed she could achieve. Notably DF was even slower than optic ataxia patient IG when tested in this same task (baseline reaching duration in static trials of DF was 809.7 ms, compared with 430 ms for IG static trials; McIntosh et al., 2011).

Remarkably DF was severely impaired in her ability to make fast trajectory corrections on jump trials whilst maintaining fixation. None of DF's corrections emerged within 400 ms after the target jump, whilst the vast majority of corrections in controls were visible within 250-300 ms (Fig. 3A and B). Her mean correction time was abnormally long

(Figs. 3C) for both left and right target jumps (left: Bayesian one-tailed p = 0.00008, Z-CCC = 8.15; right: Bayesian one-tailed p = 0.0001, Z-CCC = 7.60). The successful corrections that she made tended to be less accurate than those of controls, but this difference was not significant (left: DF = 2.78°; controls mean = 0.39°, SD = 1.04°; Bayesian two-tailed p = 0.38, Z-CCC = 1.19; right: DF = -2.65°; controls mean = -0.17°, SD = 0.74°; Bayesian two-tailed p = 0.07, Z-CCC = -2.73). Unsurprisingly, her end-point accuracy was normal for static trials (DF = 0.01°; controls mean = 0.05°, SD = 0.2°; Bayesian two-tailed p = 0.80, Z-CCC = 0.35).

In the perceptual task, DF was able to correctly discriminate the direction of the target jump when it moved rightwards (DF = 97%; controls mean = 97.2%, SD = 3.7%; Bayesian one-tailed p = 0.17, Z-CCC = 1.29), but missed a significant number of left jumps (DF = 90%; controls mean = 98.1%, SD = 2.0%; Bayesian one-tailed p = 0.01, Z-CCC = -3.60). In addition, DF showed abnormally slow perceptual discrimination of target jumps in either direction (left: Bayesian one-tailed p = 0.008, Z-CCC = 3.88; right: Bayesian one-tailed p = 0.003, Z-CCC = 2.86) (Fig.3E).

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Figure 3 about here

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3.3. Discussion

For the first time, we investigated DF's ability to react to a sudden change in target position during reaching. We found that she is dramatically unable to make fast corrections to target jumps to extra-foveal vision, in either direction. She did eventually correct on a majority of occasions, but her correction time was more than twice that of controls. She can thus guide

movements to targets in central vision quite well, but is impaired at quickly updating those movements when the target position changes. This deficit parallels that exhibited on the same task by optic ataxic patient IG, who has bilateral parieto-occipital lesions; indeed, DF's deficit is if anything more extreme that IG's (McIntosh et al., 2011).

DF was also abnormally slow in a perceptual version of the double-step task, matched for stimulus events. Unlike the simple target detection of Experiment 1, the present perceptual task required discrimination of the *direction* of the target jump. In the case-study of IG, her discrimination times were within normal limits for the stimulus conditions that DF completed here, although her performance was abnormal for some other stimulus combinations. However, IG completed more stimulus conditions in total (two jump directions by three fixation positions), and it was possible to observe a tight correlation between the visuomotor and perceptual impairment across conditions, suggesting a common functional basis (McIntosh et al., 2011). The same correlation cannot be investigated for DF, because a reduced experimental design (two jump directions by one fixation position) was used to focus on the main features of interest. However, in reaching and detection tasks alike, DF was relatively more slowed in responding to left than to right target jumps, which would certainly not exclude a common functional basis. As in Experiment 1, then, it is possible that DF's perceptual, as well as her visuomotor abnormalities, derive from her dorsal stream lesions. These data also challenge the view that DF's perceptual performance in peripheral vision should always be worse than her visuomotor control (e.g. Whitwell, Milner & Goodale, 2014).

Here, we have used a particularly stringent version of the double-step reaching task, in which fixation must be maintained at the original target location. Although normal participants do make rapid corrections in this task while holding the eyes still, the more natural inclination is to follow the target jump with the eyes slightly leading the hand

(Blangero et al., 2008). Blangero and colleagues indeed suggested that one patient (CF) with optic ataxia was able to make trajectory correction *only* after he had moved his eyes. It should be noted that the requirement to fixate is not a necessary condition to expose an on-line correction deficit. Blangero and colleagues (2008) measured but did not constrain eye movements, and the original demonstrations of an on-line correction deficit in patient IG were made with free vision (Gréa et al., 2002; Pisella et al., 2000). Thus it is interesting to test DF's on-line correction in this more naturalistic way, with no requirement to hold fixation.

The task we employed here was clearly highly demanding for DF, as she not only struggled to make fast on-line corrections but was also unable to comply with the basic speed requirement for reaching, suggesting she found the task extremely challenging. Therefore, in Experiment 3, we re-tested DF's on-line correction ability, allowing her to move her eyes and put less emphasis on speed requirements. Furthermore, we asked whether she makes trajectory corrections automatically, when the task does not require it. For this purpose, we used the STOP task of Pisella et al (2000), which instructs the participant to stop an ongoing reach as soon as they see the target jump. Healthy controls show rapid, uninstructed, corrections toward the jumped location, which precede the slower, voluntary STOP response (Pisella et al., 2000; McIntosh et al., 2011; Rossit et al., 2009; 2012). Pisella et al., however, found that patient IG made no uninstructed corrections, bolstering the idea that an automatic visuomotor feedback loop is switched off in optic ataxia. Our goal was thus to establish whether the only corrections DF can make are slow and voluntary or whether she does make automatic corrections but these are retarded.

4. Experiment 3: On-line reaching correction, in free vision

4.1. Methods

4.1.1. Participants

Patient DF who suffers from visual form agnosia (see section 2.1.1 for details) performed this experiment on the same day and place as Experiment 1 (she was 56 at the time of testing).

Control group: Six right-handed and age-matched control participants (mean age: 61.7, SD 5.2; age range: 55-68 years; 4 females) were tested (none of them were tested in Experiment 1). All participants had normal or corrected to normal visual acuity with no history of neurological conditions. All experiments were approved by the local ethical committee and all participants (including patient DF) gave informed consent prior to the study.

4.1.2. Apparatus and stimuli

The set-up, motion-tracking recordings and reaching targets were the same as in Experiment 1 (see section 2.1.2 for details), except that the following positions were used: −4 cm (left hemispace) or + 4cm (right hemispace) with respect to the central target (0) located at 40 cm distance directly in front of the start trigger. Throughout this experiment eye movements were unrestricted.

4.1.3. Procedure

The paradigm consisted of location-go vs. location-stop conditions, previously used with a large sample of healthy and brain-damaged participants (Rossit et al., 2008, 2012). At the start of each trial, the participant's right index finger rested on the start button, aligned with the subject's sagittal midline. In the location-go condition, participants were asked to point to a target, which could jump unexpectedly to the right or left side of its initial central position (30% of trials). Participants were instructed to point to the target, even if it jumped to a new location. In the location-stop condition, participants were instructed to stop their movement and return to the start position, as soon as possible, if they saw the target jump. On each trial,

participants pressed the start trigger to initiate central target presentation. One second later, a 500 ms tone (800 Hz) cued participants to start the reach. For both conditions, the target jump was triggered by release of the start trigger, i.e., at movement onset. One second after the release of the start trigger, the target disappeared and another tone announced the end of the trial. Participants were instructed to perform their movements as quickly and as accurately as possible, with their right index finger.

The two conditions (location-go; location-stop) were given in separate blocks and block order was the same across participants so that controls performed the experiment in the same order as DF (location-go followed by location-stop). Each block contained 18 practice trials (6 for each target position) and 200 experimental trials. To minimize anticipatory trajectory adjustments, target positions were unperturbed in 70% of experimental trials in each block (i.e., N = 140 trials). For the perturbed trials in each block (i.e., N = 60 trials), the target jumped in equal proportion to the right (i.e., N = 30 trials) or left (i.e., N = 30 trials) of the central target, as soon as the participant released the start button. Trial order within blocks was randomly shuffled. At the end of the experiment, calibration coordinates were obtained by continuous presentation of each target position, one by one, allowing the subjects to adjust their terminal fingertip position until they felt that they had perfectly occluded the target. There were three calibration trials per target and three for the start position.

4.1.4 Data analysis

The data analysis routine was the same as in Rossit et al. (2012). The raw data from the marker were filtered by a dual-pass through a second-order Butterworth filter with a cut-off frequency of 10 Hz, and analysed using customized software written in the LabVIEW programming environment (National Instruments).

For the location-go condition, movement offset was defined as the final frame before which forward (Y) velocity fell below 50 mm/s. For the location-stop condition, the end of

the movement was identified as the frame before the velocity in the y-axis went negative (i.e., pullback) provided that velocity fell below -100 mm/s within 50 ms of the first becoming negative. The presence of corrections in each perturbed trial was determined on spatial grounds, by comparison of the XY path of the movement (trajectory in the plane of the box surface) against the distribution of XY paths in the corresponding unperturbed trials. This analysis was conducted using the filtered XY data for each participant separately. First, XY trajectories for all movements were normalized using linear interpolation to estimate the horizontal (X) coordinate of the marker at standardized 1 mm increments along the depth (Y) axis. Second, the unperturbed trials mean x coordinate and its standard deviation were calculated at each depth increment. Next, for each normalized perturbed trajectory, the horizontal coordinate at each of these depth coordinates was classified as 'corrected' if it fell at least 2.81 standard deviations from the mean of the corresponding unperturbed trials in the direction of the target perturbation (one-tailed alpha level of 0.0025 per comparison, matching the one used in McIntosh et al., 2011 and Rossit et al., 2012), being otherwise classified as 'uncorrected'. The depth coordinates at which transitions between uncorrected and corrected states occurred were then converted to times of transition by referencing the filtered XY data for that trial and using linear interpolation to estimate the times at which the marker occupied those depth coordinates.

For corrected trials, and based on the above criteria, we defined correction time for both location-go and location-stop conditions as the time (in ms) at which the marker was first detected to be in a corrected position. For successfully corrected trials as well as for non-perturbed trials in the location-go condition we also extracted the directional error (defined as the signed angular deviation of the movement endpoint relative to the ideal reach [obtained from calibration trials]). For the location-stop condition, trials were classified as successful stops if a velocity reversal in the y-axis was detected and this was used to compute stop status

(defined as the percentage of successful stops) and stop time (defined as the time between movement onset and the time it took the subject to stop the movement). In addition, for both conditions, a temporal profile of current percentage of corrections was compiled for left and right target shifts. Time from movement onset was divided into 10 ms bins. For each time bin, the number of perturbed trials in which the marker was in a corrected position at the end of that bin was expressed as a proportion of the total number of movements in that condition that were still ongoing at the end of that time bin. The resultant profile thus recorded the current percentage of ongoing movements that were in a corrected position at each time bin. The patient's performance was compared to that of the controls using modified t-tests developed for single-case studies (Crawford & Garthwaite, 2002). Moreover the RSDT (Crawford & Garthwaite, 2005) was used to compare the left-right asymmetry in DF vs. controls and to compare differences between tasks in DF vs. controls. One-tailed tests were used for tests in which there was an unambiguous directional prediction, but not where impaired performance could differ in either direction from controls.

4.2. Results

In the location-go condition, patient DF ultimately achieved 100% of corrections in response to both right and left target jumps but her movement time was long (Figs.4A and 4B). In particular, and similarly to Experiment 2, DF's movement time (ms) was considerably longer than that of controls for static trials (DF = 602.0; controls mean = 461.5, SD = 47.5, t = 2.7, one-tailed $p = 0.02$), for left jumps (DF = 711.7; controls mean = 535.4, SD = 28.2, t = 5.2, one-tailed $p = 0.0017$), and for right jumps (DF = 607.7; controls mean = 508.9, SD = 28.8, t = 3.2, one-tailed $p = 0.01$). Moreover, as in Experiment 2, her correction time occurred significantly later than that of controls for both left (t = 5.1, one-tailed $p = 0.002$; Figs. 4A and 4C) and right target jumps (t = 3.2, one-tailed $p = 0.01$; Figs. 3A and 3C). DF was as

accurate as controls in her reaches to left and right target jumps as well as in the static trials condition (static trials: DF = -0.1°; mean controls = -0.1°, SD = 0.2°; t = 0.2, two-tailed p = 0.8; left jumps: DF = 0.2°; mean controls = -0.1°, SD = 0.2°; t = 1.4, two-tailed p = 0.2; right jumps: DF = 0.9°; mean controls = -0.1°, SD = 0.6°; t = 1.7, two-tailed p = 0.1).

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Figure 4 about here

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In the location-stop condition, despite being instructed to stop and pull back in response to a target jump all participants (including patient DF) still corrected their movements towards right and left jumps in the majority of jump trials (Fig. 5A and B). However, and similarly to the location-go condition, DF was significantly slower than controls in her correction time to both left (t = 16.5, one-tailed p = 0.00001; Fig. 5C) and right target jumps (t = 3.7, one-tailed p = 0.007; Fig. 5C). Moreover, the RSDT showed that the difference between DF's correction time to left vs. right target jumps was significantly larger than that of controls (mean difference DF = 345.3 ms; mean difference controls = 49.0 ms; t = 13.9, one-tailed p = 0.00002), indicating that she had abnormally long correction time to left jumps (Fig. 5C).

Nevertheless, despite the significant slowing of her on-line corrections, DF was able to stop her movements in response to target jumps in a similar way to controls (left jumps: t = 0.2, one-tailed p = 0.4; right jumps: t = -0.4, one-tailed p = 0.4). In particular, she stopped her movements in 90% of left jump trials (mean controls = 83%, SD = 28%) and in 82% of right jump trials (mean controls = 89%, SD = 19%) and her stop time was within the normal range for both sides of space (left jumps: DF = 522.8 ms, mean controls = 425.0 ms, SD controls =

87.8 ms, t = 1.0, one-tailed p = 0.2; right jumps: DF = 482.3 ms, mean controls = 402.2 ms, SD controls = 74.0 ms, t = 1.0, one-tailed p = 0.2) with no significant left-right asymmetry (RSDT t = 0.08, one-tailed p = 0.5).

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Figure 5 about here

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4.3. Discussion

This experiment investigated DF's ability to perform on-line corrections in response to target jumps in the less restricted condition of free vision and in a less speed-demanding task than Experiment 2. In addition we also assessed her 'automatic pilot' for the hand using the STOP task of Pisella et al (2000). Despite the relaxation of the fixation and speed requirements, DF's on-line corrections to left and right target jumps were still abnormally slow when compared to the controls. This constitutes the first demonstration that, similarly to optic ataxia patients, DF's fast on-line control is markedly impaired even when eye movements are permitted (Pisella et al., 2000; Gréa et al., 2002).

However, unlike what has been reported in optic ataxic patient IG (Pisella et al., 2000), DF still produced automatic reaching corrections in the majority of jump trials when instructed instead to interrupt her movements. This finding suggests that the 'automatic pilot' for the hand may be present in DF, since corrections emerge when not specifically instructed. However, DF's uninstructed corrections were significantly slower than controls, indicating that her 'automatic pilot' for the hand is not functionally intact. We thus confirm that, in addition to misreaching and impaired grip scaling (Hesse, Ball & Schenk, 2012), DF has a

further characteristic symptom of optic ataxia: a very slow 'automatic pilot' of the hand (Pisella et al., 2000).

In addition, and just like optic ataxia patient IG (Pisella et al., 2000), DF could voluntarily stop her movement in response to the target jumps as quickly as controls. This indicates that her impairments in on-line control of reaching are not just simply explained by a general slowing of visual or motor processing (at least in free vision). Notably this does not contradict the findings of impaired perceptual performance in Experiment 2 perceptual task since for that DF not only had to detect the jump but also discriminate its direction.

5. General Discussion

The present data question the long-standing assumption that DF's dorsal visual stream is functionally intact and that her on-line visuomotor control is unimpaired (Milner et al., 1991; Goodale, Milner, Jakobson & Carey, 1991; Goodale, Meenan et al., 1994; James et al., 2003; Whitwell, Milner & Goodale, 2014). Instead our data, along with those of Hesse, Ball and Schenk (2012, 2014), indicate that, in addition to visual form agnosia, DF also has visuomotor symptoms of optic ataxia. We confirm earlier reports that DF is impaired in peripheral (but not central) reaching, the typical diagnostic task for optic ataxia (Hesse, Ball & Schenk, 2012, 2014). Moreover, and for the first time, we find that DF also presents significant deficits in the fast on-line control of reaching, which is another common feature of patients with optic ataxia (McIntosh et al., 2011; Pisella et al., 2000; Rossetti, Pisella & Vighetto, 2003; Gréa et al., 2002; Blangero et al., 2008). This deficit was most severe when DF had to maintain central fixation, so could not acquire the displaced target with her eyes to guide her hand, yet she was also extremely slow to respond to target displacements even when eye movements were unconstrained.

We would suggest that, given the clear correspondence to established patterns of optic ataxia, the most likely explanation for DF's bilateral visuomotor problems on these tasks is that SPOC is neither anatomically nor functionally intact in either of her hemispheres (Milner et al., 1991; James et al., 2003; Bridge et al., 2013). In line with this, DF's peripheral reaching performance, with increasing errors towards fixation at larger target eccentricities, is not only reminiscent of optic ataxia, but is also akin to that of healthy participants who have undergone rTMS to SPOC (Vesia et al., 2010; Ciavarro et al., 2013). Moreover, the same SPOC regions that are damaged in patients with optic ataxia (Karnath & Perenin, 2005), have been shown to be activated in healthy participants during reaching, especially towards peripheral targets (Prado et al., 2005; Martin, Karnath & Himmelbach, 2015). Similarly, monkey neurophysiology has shown that neurons in V6A, an area in the macaque thought to correspond to human SPOC, are particularly sensitive to arm movements directed to non-foveated objects (Marzocchi et al., 2008), are modulated by gaze position (Galletti, Battaglini & Fattori, 1995) and, when inactivated, lead to misreaching to peripheral targets (Hwang et al., 2012). Moreover, inactivation, neuroimaging and neurophysiological studies in both human and non-human primates have also implicated the posterior parietal cortex in on-line corrections of hand movements (Desmurget et al., 1999, 2001; Diedrichesen et al., 2005; Reichenbach et al., 2011; Tunik, Frey & Grafton, 2005; Tunik et al., 2007; Battaglia-Mayer et al., 2013, 2014; Archambault, Caminiti & Battaglia-Mayer, 2009; Archambault et al., 2015; Gaveau et al., 2014; Glover, Miall & Rushworth, 2005; Rice, Tunik & Grafton, 2006; Rice et al., 2007; Della-Maggiore et al., 2004; Rossit et al., 2012).

DF was also impaired when detecting peripheral targets perceptually and when discriminating jump direction. It could thus be argued that DF's deficits in peripheral reaching to static and jumping targets may be a consequence of her perceptual impairments rather than visuomotor symptoms *per se*. However, it has recently become apparent that

patients with optic ataxia – without ventral stream involvement - show similar perceptual deficits, which may reflect impaired orienting of attention to optic ataxic fields (Striemer et al., 2007, 2009; Pisella et al., 2007; McIntosh et al., 2011). Moreover, neurophysiological recordings in the monkey have shown that attentional and reach activity are closely related in area V6A (Galletti et al., 2010) and, that rTMS over human SPOC selectively impairs attentional orienting in both reaching and attentional tasks (Ciavarro et al., 2013). Furthermore, in Experiment 3, DF had a significant asymmetry in correction time when compared to controls with severe slowing for left jumps specifically. Similarly, we found that her performance was also asymmetric in the perceptual discrimination task in Experiment 2. DF's asymmetrical pattern is reminiscent of the slow correction times for left jumps we have found in patients with left visual neglect after right temporo-parietal strokes (Rossit et al., 2012). Thus it could be that DF's lesions also cause a deficit in our perceptual tasks due to a problem in attention orienting which is more severe for the left side of space, but this remains to be tested.

The present findings, and those of Hesse et al (2012, 2014), are at odds with a previous report of spared peripheral reaching performance in DF (Milner et al., 1999). It has been suggested that DF's lesion in the dorsal stream may have increased since her first scans (Whitwell, Milner & Goodale, 2014) thus explaining why only now she is found to be impaired in peripheral reaching. However, an alternative possibility is that perhaps in Milner et al. (1999)'s experiment, patient DF may have erroneously moved her eyes towards the target rather than keep fixation thus explaining her spared performance on their reaching task. In other words, it could be that DF's visuomotor control may have never been completely intact. In any event, given the pivotal role that the putative dissociation between optic ataxia and visual form agnosia has played in supporting the perception-action model, it is important

to consider what implications these findings have for that dissociation, for the model, and for the testing of DF herself.

We conclude that DF, one of the cornerstones of the perception and action model, should no longer be considered a pure visual form agnosia patient who has suffered exclusive ventral stream damage. In particular, we can no longer assume that DF's dorsal visual stream is intact and that she is spared in visuomotor control tasks, as she also presents clear signs of optic ataxia. This highlights how correct Rossetti, Pisella and Vighetto (2003) and Pisella et al. (2006) were to point out the lack of parallel testing of optic ataxia and visual form agnosia. However we would argue that the finding that DF has optic ataxia does not necessarily exclude the possible existence of a dissociation between visual form agnosia and optic ataxia, in contrast to what has been suggested by Hesse et al. (2012, 2014). Instead we simply suggest that the dissociation hasn't actually been properly tested and that her concomitant optic ataxia makes her an inappropriate participant for the testing of visuomotor function in visual form agnosia, and thus for the dissociation between optic ataxia and visual form agnosia.

These new revelations have significant implications for previous studies of patient DF (including our own) which have attributed her deficits to ventral stream damage and, thus their conclusions should be revisited to acknowledge a dorsal involvement as well. It is also important to admit that attributing certain symptoms to lesion location is very difficult in patient DF as she presents large ventral and dorsal visual stream lesions as well as widespread brain atrophy. In fact, Milner et al. (1991) already noted that DF also presents bilateral basal ganglia (i.e., globus pallidus and lentiform nucleus) damage, which can be associated with inaccurate reaching in open loop conditions and increased reaction times (Rossit et al., 2009) as well as on-line control of error corrections (Grafton & Tunik, 2011). Therefore, this subcortical damage in DF, along with the presence of both perception and

action deficits in this patient, generates significant difficulties in using her as a single-case patient model to test the neural basis of perception and action. It does not, however, diminish the scientific interest in contrasting further, more pure cases, of visual form agnosia with optic ataxia.

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Figure captions

Figure 1. Results of experiment 1. End-pointing coordinates of patient DF and average of the control participants per target position for free and peripheral vision. Negative x-coordinates denotes left side of space and positive x-coordinates the right side of space.

Figure 2. Results of experiment 1. Mean directional error (in degrees) for patient DF and control participants per target position for free (A) and fixation conditions (B). C. Mean reaction time (in ms) for the perceptual task with fixation for patient DF and control participants. Error bars represent control 95% confidence intervals calculated with single-case statistics (Crawford & Garthwaite, 2002). CI = confidence interval.

Figure 3. Results for experiment 2. (A and B) Current proportion of corrected responses to left (A) and right (B) peripheral jumps for patient DF and controls. Dotted lines represent

95% control confidence interval (lower bound only). (C) Mean correction time (in ms) for DF and controls. (D) Mean reaction time (in ms) for the perceptual task for patient DF and control participants. (C to E) Error bars represent control 95% confidence interval. (A to D) All control confidence intervals were calculated with single-case statistics (Crawford & Garthwaite, 2002). CI = confidence interval.

Figure 4. Results for the location go condition (experiment 3). (A and B) Current proportion of corrected responses to left (A) and right (B) jumps for patient DF and controls. Dotted lines represent control 95% confidence interval (lower bound only). (C) Mean correction time (in ms) for DF and controls. Error bars represent control 95% confidence interval. (A to C) All control confidence intervals were calculated with single-case statistics (Crawford & Garthwaite, 2002). CI = confidence interval.

Figure 5. Results for the location stop condition (experiment 3). (A and B) Current proportion of corrected responses to left (A) and right (B) jumps for patient DF and controls. Dotted lines represent control 95% confidence interval (lower bound only). (C) Mean correction time (in ms) for DF and controls. Error bars represent control 95% confidence interval. (A to D) All control confidence intervals were calculated with single-case statistics (Crawford & Garthwaite, 2002). CI = confidence interval.

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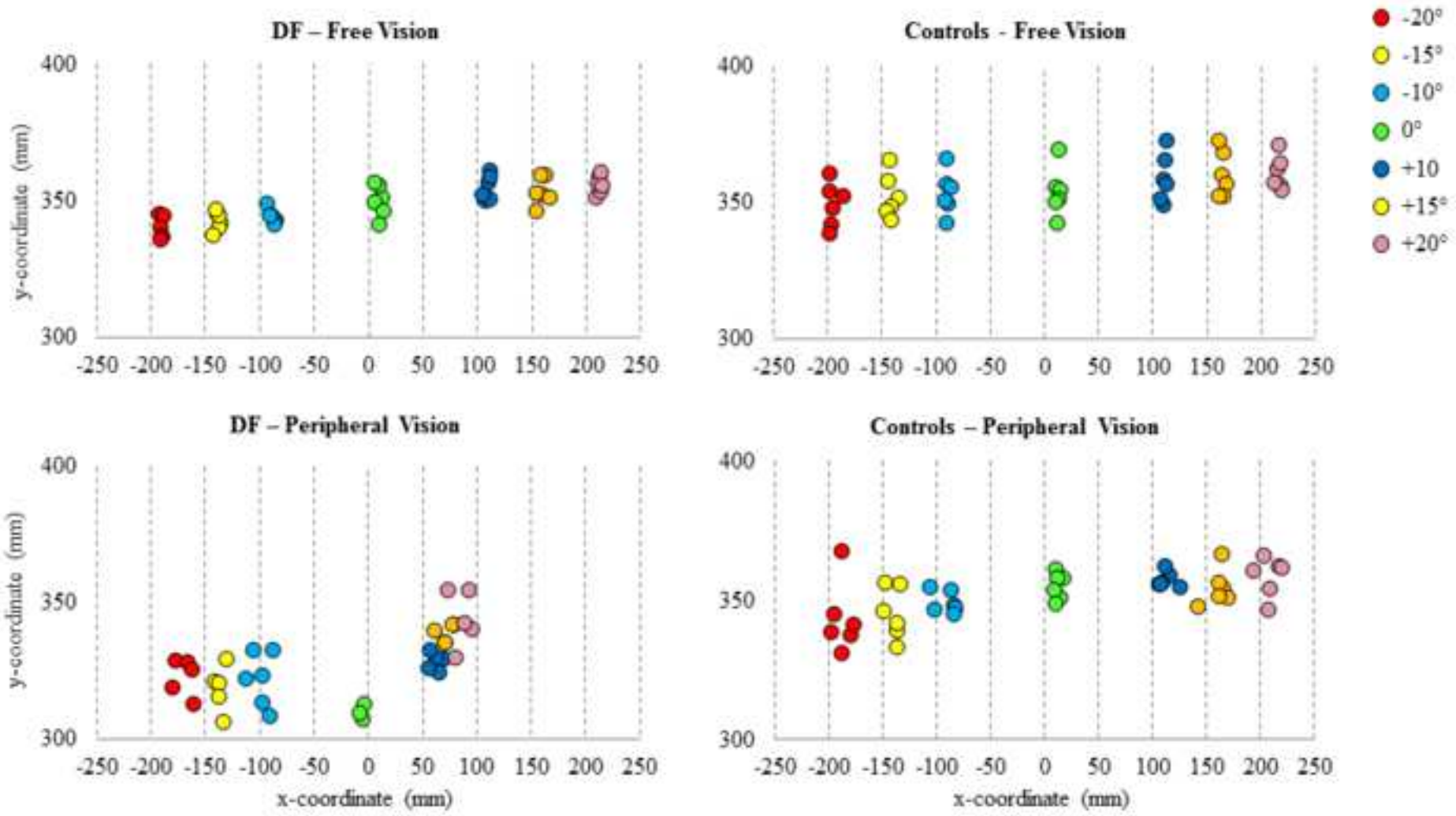

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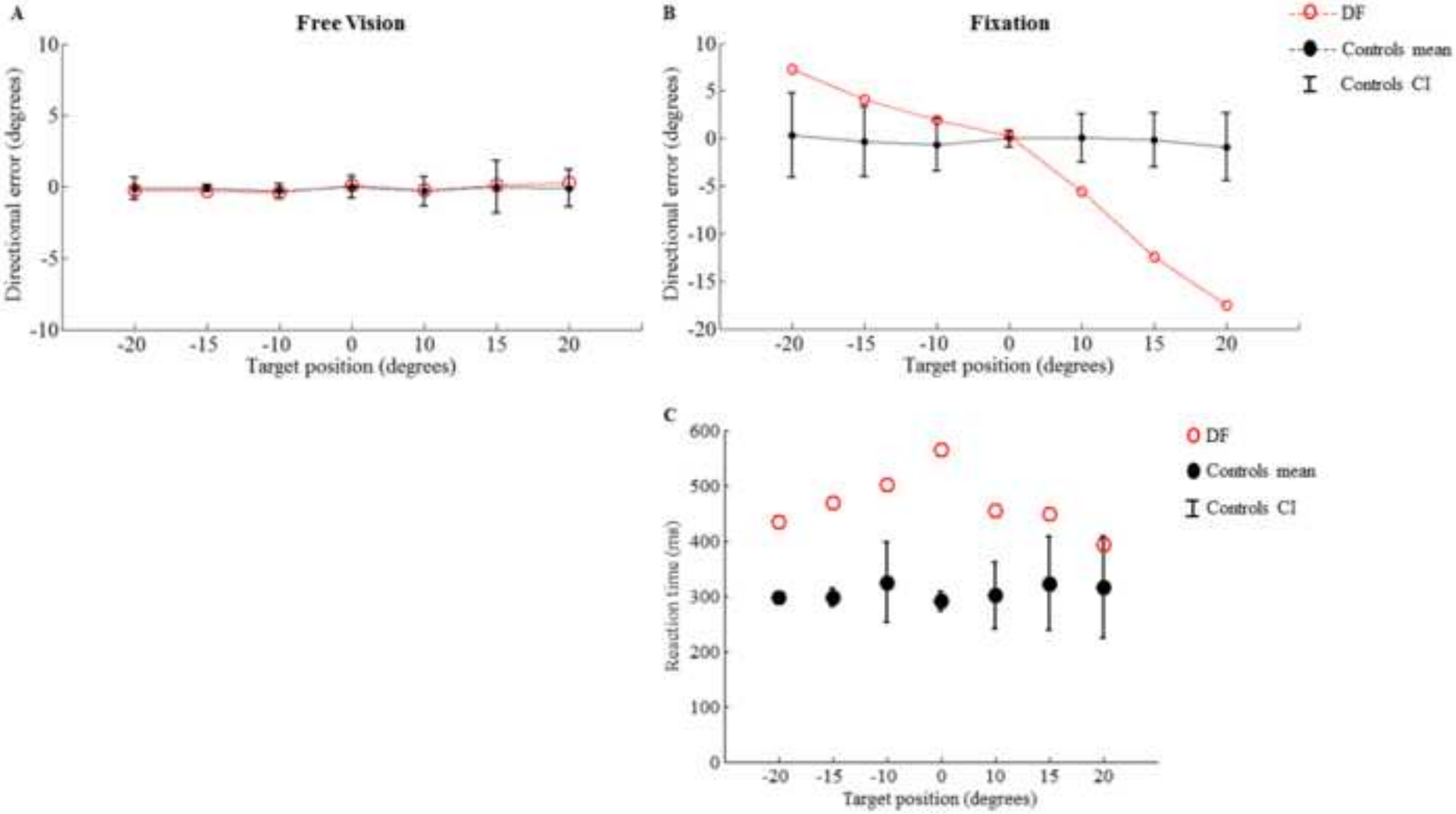

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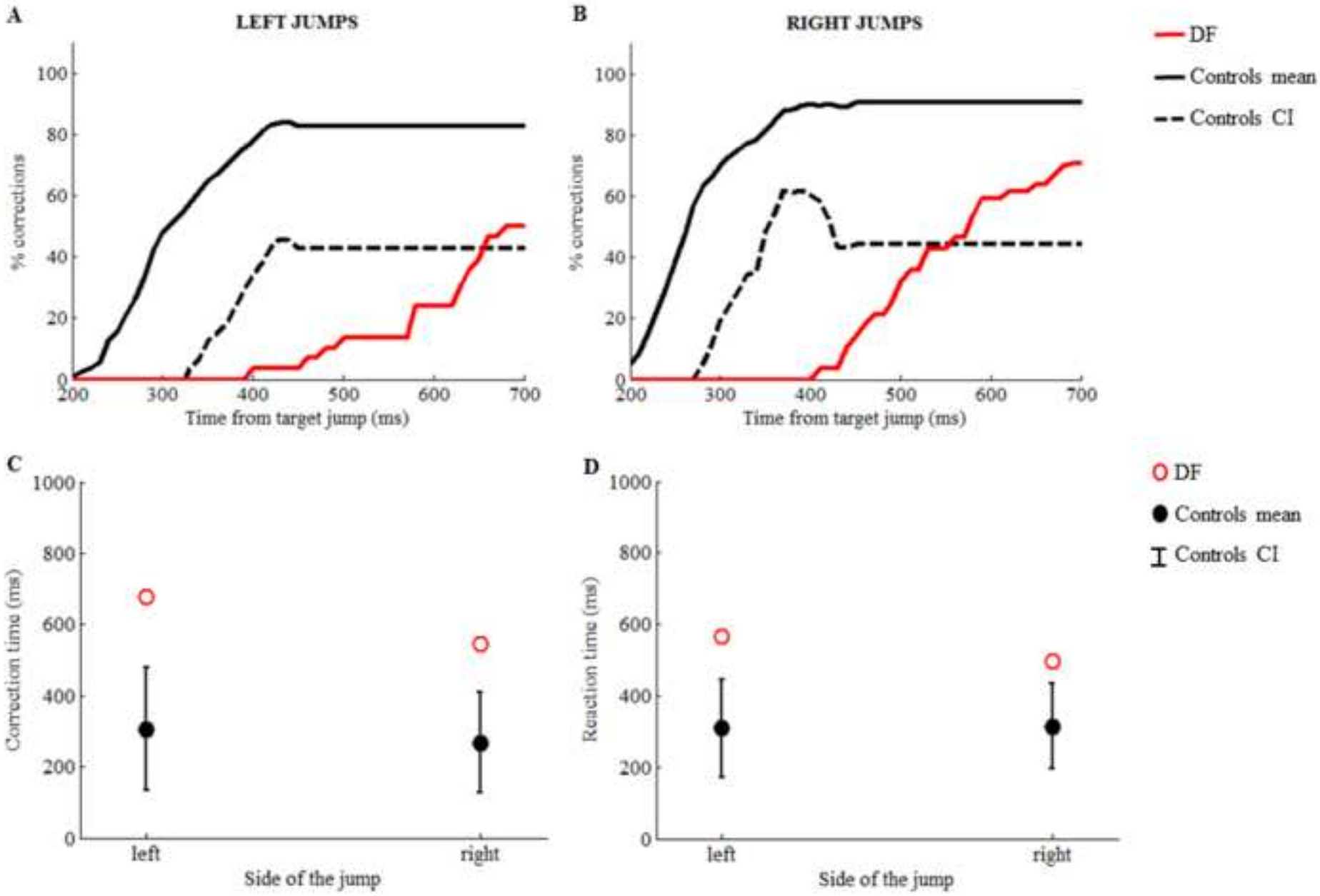

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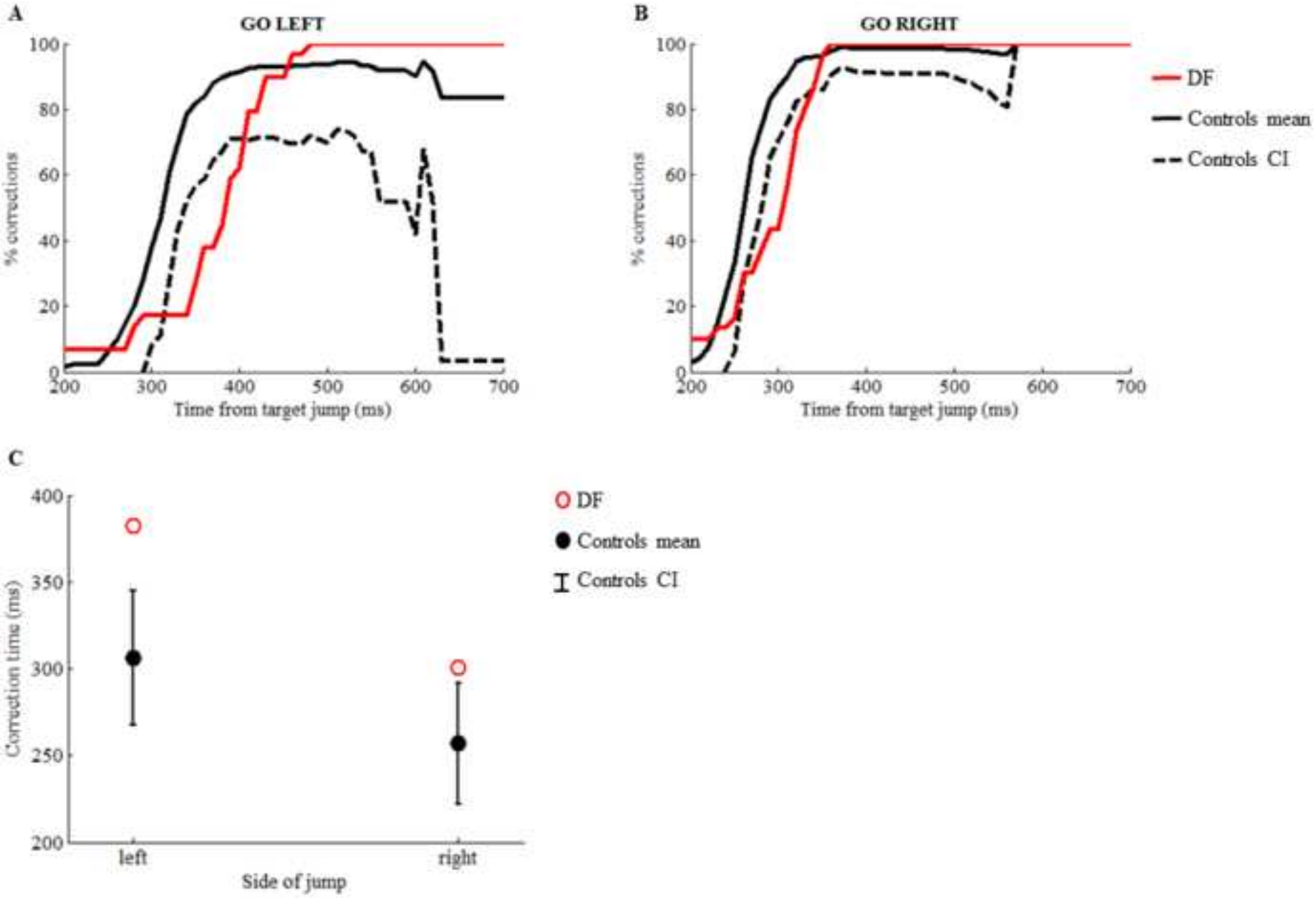

Rossitetal_Figure 5

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