

Hemispheric asymmetry and callosal integration of visuospatial attention in schizophrenia: A tachistoscopic line bisection study

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Abstract

Background: A hallmark of visuospatial neglect syndrome is that patients with lesions to right parietal cortex misbisect horizontal lines far rightward of veridical center. Neurologically normal subjects misbisect lines with a systematic leftward bias (pseudoneglect). Both phenomena, as well as neuroimaging studies, disclose a predominant right-hemisphere control of spatial attention. Numerous studies of patients with schizophrenia have implicated global deficits of either right or left hemisphere function, as well as compromised integrity of the corpus callosum.

Methods: To better understand the functional implications of schizophrenia we utilized a forced-choice tachistoscopic line bisection task to probe the status of right-hemisphere control of spatial attention, and compared left- versus right-hand unimanual responses to index the degree of callosal transfer of visuospatial information in both patient and control groups.

Results: In contrast to the significant leftward bisection errors of control subjects, patients exhibit no significant leftward error. Whereas control subjects evince a significant correlation between left- and right-hand bisection errors, patients lack a significant intermanual correlation.

Conclusions: The lack of significant leftward bisection error of patients implies a deficit of right-hemisphere function. The lack of a significant correlation between left- and right-hand bisection errors in patients implies a loss of callosal integrity.

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1. Introduction

1.1. Visuospatial neglect and pseudoneglect

Visuospatial attention refers to that type of environmental monitoring which is deployed across the visual field. Disruptions of visuospatial attention are a hallmark of the clinical neurological syndrome known as

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hemispatial neglect, which is associated with vascular lesions of the right parietal and/or temporal–parietal–occipital (TPO) cortex (Cappa et al., 1991; Kerkhoff, 2001; Mesulam, 1982; 2000; Na et al., 2000; Vallar and Perani, 1987). Line bisection is a frequently used task for the clinical assessment of hemispatial neglect. In line bisection tasks subjects manually mark, or otherwise indicate, the perceived midpoint of lines. Patients with hemispatial neglect bisect horizontal lines far rightward of veridical center (Heilman et al., 1993; Mesulam, 2000; Robertson and Halligan, 1999). Converging evidence from both the laboratory and the clinic indicates that neural circuits in the right cerebral hemisphere play a dominant role in the allocation of visuospatial attention (Corbetta et al., 2000; Coull et al., 2001; Fink et al., 2000; Foxe et al., 2003; Karnath, 2001; Karnath et al., 2001). That the right hemisphere is dominant for this function is revealed in dramatic fashion by the severe deficits of attention directed into contralesional (left) space in hemineglect syndrome (Cappa et al., 1991; Kerkhoff, 2001; Mesulam, 1982; 2000; Na et al., 2000; Vallar and Perani, 1987). The paucity of leftward-directed attention leads to gross rightward errors on line bisection tasks.

There is general agreement that whereas both hemispheres participate in the deployment of spatial attention to right hemispace, the right hemisphere is uniquely responsible for allocating attention into left hemispace (Heilman and Van Den Abell, 1980; Weintraub and Mesulam, 1987). Thus, lesions to the right hemisphere frequently render neglect patients pathologically inattentive to left hemispace, whereas lesions to homologous regions of the left hemisphere produce only modest deficits of spatial attention.

The hemispheric specialization hypothesis of neglect is further supported by the phenomenon known as “pseudoneglect” (Bowers and Heilman, 1980; Jewell and McCourt, 2000), which refers to the systematic leftward misbisection of horizontal lines made by neurologically intact observers. The theoretical connection is that pseudoneglect is proposed to result from the same profound asymmetry in the magnitudes of the attentional vectors projected into left versus right hemispace that underlie hemineglect syndrome (Mccourt and Jewell, 1999; McCourt et al., 2000, 2001a,b).

1.2. Line bisection in patients with schizophrenia

Five studies to date have reported line bisection performance in patients diagnosed with schizophrenia. The earliest study (Mather et al., 1990) reported a

significant leftward bisection error for control subjects, and no significant difference between the patient and control groups. A study by Barnett (2006) also found leftward errors for control subjects, but the errors made by patients did not differ significantly from zero. Two studies from the same laboratory (Cavezian et al., 2007; Michel et al., 2007) reported bisection errors in control subjects that were not significantly different from zero, and significant leftward errors for patients. Finally, Zivotofsky et al. (2007) reported bisection errors in patients diagnosed with schizophrenia which were not significantly different from zero. Obviously, there is considerable disagreement with respect to both data and interpretation across these studies. It should be noted that all of the previous studies utilized method-of-adjustment manual line bisection procedures which require subjects to make gross motor gestures using the hand and arm, and allow for unlimited oculomotor scanning of the line stimuli. Oculomotor or limb scanning is a significant contributor to bisection error, as disclosed by a recent meta-analysis (Jewell and McCourt, 2000), and unilateral motor activity has also been shown to significantly affect bisection error (Mccourt et al., 2001a). When gross motor activation is minimized, and scanning eye movements are disallowed by tachistoscopic presentation, the effect size (Cohen’s *d*-statistic; Cooper and Hedges, 1994) of pseudoneglect is tripled relative to that found using manual line bisection procedures ($d = -1.32$ versus -0.40 , respectively; Jewell and McCourt, 2000). In addition, most of the prior studies tested only a modest sample of patients: $N = 24$ (Mather et al., 1990); $N = 10$ (Barnett, 2006); $N = 8$ (Michel et al., 2007); and $N = 10$ (Cavezian et al., 2007). In the largest study to date, Zivotofsky et al. (2007) report data from 45 schizophrenic patients, but the lack of a control group makes interpretation of their results problematic. Finally, only Mather et al. (1990) and Barnett (2006) examined the effects of hand used to bisect; the other studies examined only unimanual responses by the dominant hand. For these reasons it is conceivable that important (and statistically significant) differences in the bisection performance of patients and controls were overlooked. The current study was therefore conducted on a large sample of patients ($N = 34$) using a tachistoscopic forced-choice visual line bisection technique. This procedure is three times more sensitive to visuospatial asymmetries than is method-of-adjustment since it minimizes the confounding influences of oculomotor and manual scanning, and isolates the contribution of perceptual/attentional mechanisms. We find that control and patient groups differ significantly

on two dimensions. The first is with respect to a global asymmetry of spatial attention, where patients fail to exhibit the typical leftward bisection error which signifies right-hemisphere dominance in control subjects. The second is with respect to intermanual coordination, where the lack of a significant correlation between left- and right-hand bisection errors in patients implies a deficit of transcallosal hemispheric integration.

2. Method

2.1. Participants

The control group consisted of twenty neurologically normal right-handed subjects (10 male; mean age=36.4 years). The patient group consisted of 34 medicated right-handed patients with a diagnosis of schizophrenia/schizoaffective disorder (28 male; mean age=37.3 years). All patients were inpatients and were recruited from the Clinical Research and Evaluation Facility (CREF) at the Nathan Kline Institute for Psychiatric Research (NKI), an inpatient and outpatient New York state psychiatric facility. Diagnosis was determined by means of chart review, consultation with physicians, and the Structured Clinical Interview for DSM-IV, SCID (First et al., 1997). Both patients and controls were excluded from participating if they exhibited any neurological or ophthalmologic disorders, or if they met criteria for substance dependence within the previous six months, or substance abuse within the month preceding testing. Laterality was assessed using a standard instrument (Oldfield, 1971; expanded scale) on which a composite score of -220 denotes exclusive left-handedness, and $+220$ denotes exclusive right-handedness. The mean laterality score of control subjects was 165.8 ; mean laterality score for patients was 185.5 . There was no significant difference between groups with respect to age, $t(52)=0.28$, $p=0.779$; the patient group scored modestly higher on the laterality index, $t(52)=2.17$, $p=0.035$.

The patient group exhibited primarily negative symptomology. See Table 1 for demographic and clinical data for the patient group.

The work described here has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Prior to their participation in the study, all participants provided written informed consent. All procedures were approved by the Institutional Review Boards of North Dakota State University and the Nathan Kline Institute for Psychiatric Research.

2.2. Instrumentation and calibration

Subject responses were sensed and collected, and stimuli were presented on a CRT, by microcomputer. Display resolution was 1024×768 pixels ($34.6^\circ \times 26.4^\circ$), and the monitor frame refresh rate was 70 Hz. The generation and sequencing of stimuli, and the collection of subject responses, were accomplished using an application written in C++ which utilized the DirectX graphics library.

2.3. Stimuli

Stimuli were horizontally oriented lines of 100% Michelson contrast presented on a homogeneous background whose mean luminance was 35 cd/m^2 . At a viewing distance of 65 cm the CRT screen subtended 34.6° (w) $\times$ 26.4° (h) visual angle; the horizontal line stimuli subtended $13^\circ \times 0.44^\circ$. All lines were pre-transected prior to presentation.

Fig. 1 illustrates examples of line stimuli. Both members of the upper pair of lines (A, B) are transected to the left of veridical line midpoint, by -0.51° and -0.05° , respectively. Both members of the lower pair of lines (D, E) are transected to the right of veridical line midpoint, by $+0.51^\circ$ and $+0.22^\circ$, respectively. Line C is transected at the veridical midpoint. The members of line pairs (A, B) and (D, E) differ in contrast polarity. Lines of each contrast polarity appeared with equal frequency throughout the experiment.

2.4. Procedure

Subjects were seated upright in straight-backed chairs with their midsagittal planes aligned with the display

Table 1
Demographic and clinical characteristics of schizophrenia patient group ($n=34$)

Characteristic	Mean $\pm$ SD
Diagnosis: schizophrenia/schizoaffective disorder	26/8
Neuroleptics: typical/atypical/both	21/3/10
Chlorpromazine daily equivalent, mg	1252.6 ± 557.8
Education, years	11.3 ± 2.2
Illness duration, years ^a	17.6 ± 9.6
IQ (quick test) score ^a	95.1 ± 9.7
BPRS positive symptom ^a	9.9 ± 4.5
SANS (total score without global baseline) ^a	26.6 ± 11.5

Abbreviations: BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms. Diagnoses were obtained using the Structured Clinical Interview for DMS-IV and all available clinical information. Doses of anti-psychotic medications were translated into chlorpromazine equivalents using the best available literature at the time of data analysis.

^a Data were missing for a single patient in each case.

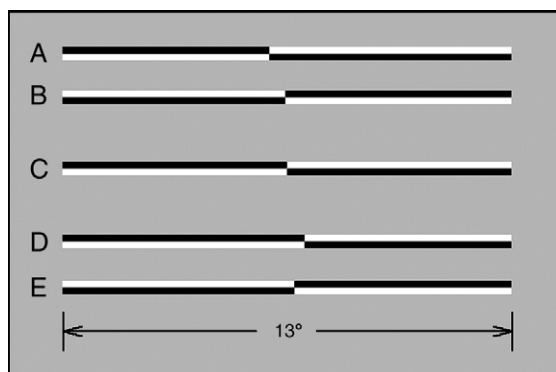


Fig. 1. Examples of line stimuli used in the experiments. The members of the upper pair (A, B) are transected to the left of veridical line midpoint (by -0.51° and -0.05° , respectively). The members of the lower pair (D, E) are transected to the right of veridical center (by $+0.51^\circ$ and $+0.22^\circ$, respectively). Line C is veridically transected. The members of line pairs (A, B) and (D, E) differ in contrast polarity. Lines of opposite polarity appeared with equal frequency and were counterbalanced within and across blocks of trials.

monitor. On each trial subjects made single-interval forced-choice decisions regarding transector location relative to perceived line midpoint by depressing either the left or right mouse button, as appropriate. Button orientation corresponded to the axis of perceptual discrimination, such that the “left” response button was situated to the left of the “right” response button. Subjects responded using both right and left hands in separate blocks of trials. The order of hand use was counterbalanced across subjects and blocks.

Tachistoscopic presentation (Mccourt and Olafson, 1997) was used to control for the possible confounding effects of scanning eye movements. Pre-transected lines were presented for 143 ms; inter-trial intervals were variable since subsequent trials began approximately 500 ms following previous responses.

Perceived line midpoint was assessed using an adaptive psychophysical staircase procedure (Cornsweet, 1962). Each block of trials incorporated ten randomly interleaved staircases. Each staircase was initiated with a transector location randomly selected to lie in the range of $\pm 0.15^\circ$ from veridical line midpoint. A one-down one-up rule was employed such that each staircase converged on the transector location producing a 50:50% left–right response rate; the transector location corresponding to a 50:50% left–right response rate is defined as the point of subjective equality (p.s.e.). From trial to trial, based on subject responses, transector location was adjusted in step sizes of 0.034° (i.e., a single pixel). Each of the ten interleaved staircases ran until six reversals were obtained. For purposes of analysis the first two reversal values in each staircase were discarded (as practice trials), and p.s.e. was

calculated as the mean of the four remaining reversal values. Subsequent inferential statistical tests were conducted on these mean p.s.e.’s. Each block of staircases was completed in approximately 200 trials. Subjects completed either one or two blocks of staircases using each hand (average number of blocks/subject = 1.8).

3. Results

Fig. 2 plots mean p.s.e (± 2 s.e.m.), for both control and patient groups, as a function of hand used to respond. Averaged across hands, bisection error measured -0.16° for controls and -0.02° for patients (negative values indicate leftward errors). A 2 (hand) $\times$ 2 (group) mixed ANOVA revealed no significant main effect of hand used to respond, $F(1, 52) = 0.066$, $p = 0.798$, and no significant hand $\times$ group interaction, $F(1, 52) = 0.154$, $p = 0.696$. There was, however, a significant main effect of group, $F(1, 52) = 5.178$, $p = 0.027$, such that control subjects demonstrated a greater mean leftward bisection error than did patients. Single-sample *t*-tests revealed that mean bisection error in control subjects deviated significantly

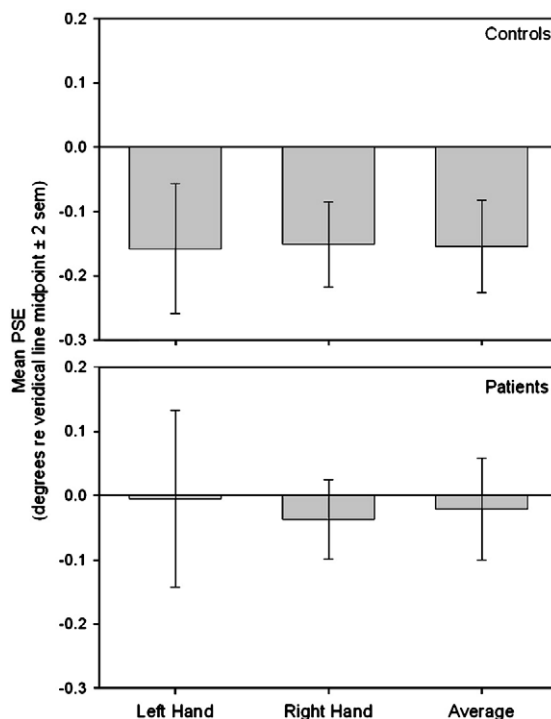


Fig. 2. Mean p.s.e (± 2 s.e.m.) is plotted for control and patient groups as a function of hand used to respond. Control subjects demonstrated a significantly greater mean leftward bisection error than did patients. Average bisection error was -0.16° for controls, and was significantly leftward of zero. Average error was -0.02° for patients and was not significantly leftward of zero.

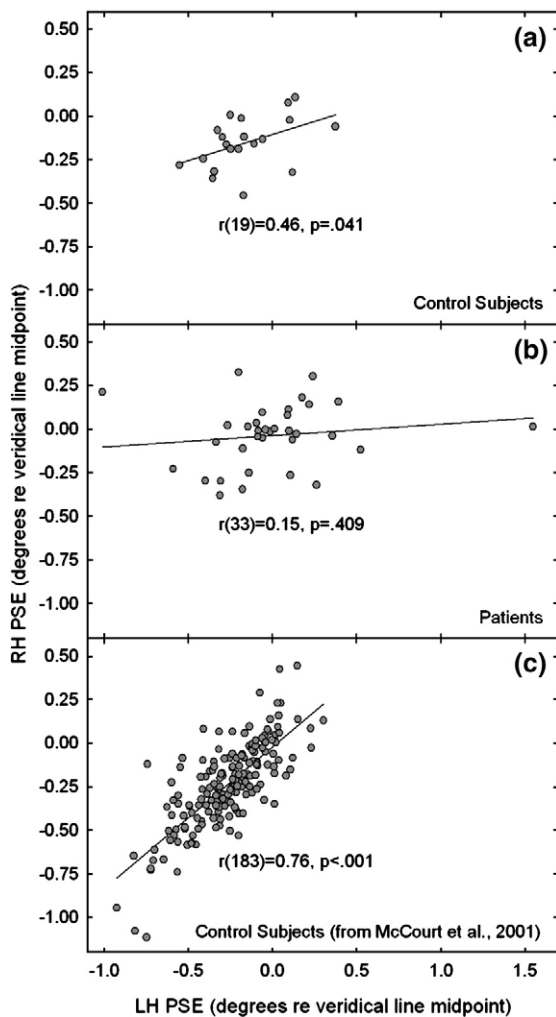


Fig. 3. Correlograms plot right- versus left-hand bisection errors (p.s.e.) for the control group (panel a) and for the patient group (panel b). There is a significant correlation between bisection errors made using the right and left hands for controls, whereas this correlation is nonsignificant for patients. Panel (c) replots right- versus left-hand bisection judgments obtained from a large group ($N=184$) of control subjects from a previously published study (Mccourt et al., 2001a) which utilized a nearly identical methodology. Intermanual correlations are significant for control subjects, but are uncorrelated for the patient group.

leftward of veridical line midpoint (zero error): Left hand, $t(19)=-3.13$, $p=0.005$; Right hand, $t(19)=-4.57$, $p<0.001$; Average, $t(19)=-4.30$, $p<0.001$. Bisections made by patients did not differ significantly from veridical line midpoint in any condition: Left hand, $t(33)=-0.66$, $p=0.948$; Right hand, $t(33)=-1.19$, $p=0.242$; Average, $t(33)=-0.52$, $p=0.606$. In addition, there were no significant ($p<0.05$) sex-related differences in bisection error for either controls or patients.

Fig. 3 shows correlograms which plot right- versus left-hand bisection errors (p.s.e.) for the control group

(panel a) and for the patient group (panel b). There is a significant correlation between bisection errors made using the right and left hands for controls, $r(19)=0.46$, $p=0.041$, whereas this correlation is nonsignificant for patients, $r(33)=0.15$, $p=0.409$. Because the number of control subjects tested in the current study is modest, panel (c) plots right- versus left-hand bisection judgments obtained from a large group ($N=184$) of control subjects from a previously published study (Mccourt et al., 2001a) which utilized a nearly identical methodology. The degree of consistency between bisections executed with the two hands in this larger control group is highly significant, $r(183)=0.76$, $p<.001$, in agreement with results from the current control group, but in stark contrast to the uncorrelated hand-related bisections exhibited by patients. Each control subject executed four separate blocks of bisection trials (two with each hand). The inter-block correlation for mean bisection errors was $r(38)=0.79$, $p<0.001$. Only twenty-two of the patient group completed all four blocks of bisection trials, but for those who did the inter-block correlation for mean bisection errors was $r(42)=0.48$, $p=0.001$. Thus, while the magnitude of inter-block correlation for patients is somewhat diminished relative to that seen in control subjects, general inconsistency of behavior in the bisection task itself is unlikely to account for the observed lack of a significant intermanual correlation.

4. Discussion

The mean leftward bisection error of the control group (-0.155° ; 1.2% line length) is comparable to that reported in numerous previous studies using the forced-choice tachistoscopic line bisection procedure (Foxe et al., 2003; McCourt and Jewell, 1999; McCourt and Garlinghouse, 2000; 2001; McCourt, 2001; McCourt et al., 2000; 2001a, b; 2005), and replicates the nearly universal finding that neurologically normal observers exhibit a modest, yet significant and systematic, leftward error on line bisection tasks, i.e., pseudoneglect; see Jewell and McCourt (2000), for a meta-analytic treatment and review of this literature. The trend for greater leftward errors of control subjects when making bisections using the left hand, while not achieving statistical significance in the present study, is also congruent with previous literature (Mccourt et al., 2001a).

The first noteworthy finding is that patients do not, as a group, exhibit the normal pattern of significant leftward bisection error (pseudoneglect) which characterizes the right-hemisphere dominance for the allocation of visuospatial attention observed in neurologically normal subjects. One interpretation of this finding is that some aspect(s) of right-hemisphere structure/function are compromised in

schizophrenia. While initial studies of schizophrenia patients identified selective deficits in functions associated with the left hemisphere (Gruzelier and Hammond, 1980; Gur and Chin, 1999; Kugler and Henley, 1979; Magaro and Chamrad, 1983; Posner et al., 1987), evidence is accumulating to suggest right hemispheric deficits as well (Barnett and Kirk, 2005; Barnett et al., 2005; Minor and Park, 1999; Mizuno et al., 1997; Murphy and Cutting, 1990). In addition to identifying global abnormalities of hemispheric function a number of recent studies has probed the integrity of specific functional neuroanatomical pathways, disclosing that schizophrenia involves selective deficits within the magnocellular (dorsal) processing stream (Butler et al., 2001; Foxe et al., 2001, 2005; Schechter et al., 2003; 2005). This is potentially significant since parietal cortex is a major recipient of magnocellular input (Merigan and Maunsell, 1993; Ungerleider and Mishkin, 1982), and houses neural networks demonstrated to play a crucial role in the allocation of visuospatial attention (Corbetta et al., 2000; Coull et al., 2001; Fink et al., 2000; Foxe et al., 1998; 2003; Karnath, 2001; Karnath et al., 2001), including those activated during line bisection tasks. Thus, deficits of magnocellular function are a likely candidate to underlie the abnormalities of spatial attention we describe. In summary, the reduction in right-hemisphere control of visuospatial attention in the patient group might accrue from either a global hemispheric dysfunction, or alternatively, from a specific magnocellular deficit. In either case, additional line bisection studies of patients utilizing the tachistoscopic forced-choice methodology, in conjunction with high-density EEG recording (see, for example, Foxe et al., 2003) would be revealing in this regard.

A second noteworthy and novel finding is that, whereas control subjects evince a highly significant correlation between bisection errors committed using the two hands (see also McCourt et al., 2001a), the patient sample exhibits a remarkable lack of intermanual correlation. This finding is intriguing since, in addition to the cited evidence that schizophrenia involves alterations of normal cerebral laterality, there is a growing consensus that patients with schizophrenia manifest structural and/or functional deficits of the corpus callosum (Barnett, 2006; Green, 1978; Mohr et al., 2000; Woodruff et al., 1995). Non-schizophrenic subjects with frank lesions of the corpus callosum exhibit a pattern of intermanual line bisection performance in which the direction of errors differs in sign when bisections are executed using the right versus the left hands (Hausmann et al., 2003a,b; Heilman et al., 1984; Wolk and Coslett, 2004). Further, callosal immaturity in young children has been suggested to explain similar dissociations of bisection error as a function of hand used to respond (Bradshaw

et al., 1988; Failla et al., 2003; Hausmann et al., 2003a,b). The absence of a significant correlation between right and left-hand bisections in our patient group strongly suggests an impairment of normal interhemispheric information transfer.

A detailed consideration of intermanual bisection performance is informative in this regard. Control subjects exhibit a highly significant correlation between left-hand and right-hand responses (Fig. 3a, c). This correlation implies that efficient callosal transfer of information pertaining to spatial attention flows from the dominant to the non-dominant hemisphere, effectively yoking the responses of both hands to the output of the dominant hemisphere. Such intermanual coordination is independent of which hemisphere happens to be dominant for spatial attention; however, the data of Fig. 2 (as well as the preponderance of evidence from line bisection research, see: Jewell and McCourt, 2000; Foxe et al., 2003) discloses that for neurologically normal subjects the right hemisphere is overwhelmingly dominant in this regard. Patients with schizophrenia, by contrast, exhibit no significant correlation between line bisection errors committed using the left and right hands (Fig. 3b). Instead, when using either hand to perform the line bisection task, patients commit bisection errors which reflect the controlling hemisphere's degree of attentional control, consistent with the activation-orientation theory of attention (Kinsbourne, 1970; 1993).

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Contributors

Authors MEM, JJF and DCJ designed the study. Author MS implemented the study, collected and scored data. Author MEM ran statistical analyses and wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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