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Research report

Visuospatial working memory is severely impaired in Bálint syndrome patients

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ABSTRACT

Although it has been proposed that visuospatial working memory may be impaired in Bálint syndrome patients, neither a systematic study concerning this proposal nor a comparison with patients having right-parietal damage has been made. Visuospatial working memory was assessed for six Bálint syndrome patients and members of two control groups—one composed of individuals with right-parietal damage ($n = 15$) and a second of age- and gender-matched healthy individuals ($n = 26$). We placed special emphasis on patients with a mild form of Bálint syndrome who can judge positional relationships between two objects. First, the participants were subjected to delayed visuospatial matching tasks. Next, their visuospatial-temporal integration abilities were assessed using a shape-from-moving-dots task. Visuospatial working memory was impaired for Bálint syndrome patients compared with controls according to the results of the tests. The differences between the Bálint syndrome and control subjects remained when only data for patients with the mild form of Bálint syndrome were included. We conclude that visuospatial working memory may be severely impaired in Bálint syndrome patients and, therefore, might influence their inability to properly execute movements and behaviours associated with daily living.

1. Introduction

Visuospatial working memory is the capacity to maintain a representation of visuospatial information for a brief period (Rizzo & Vecera, 2002). It connects working-memory components with phonological working memories (Baddeley, 1986), which are temporarily stored and accessed for use in many different cognitive tasks.

Abbreviations: HDS-R, Revised Hasegawa Dementia Rating Scale; PIQ, performance intelligence quotient; RBMT, Rivermead Behavioural Memory Test; TMT-A, Trail Making Test A; VIQ, verbal intelligence quotient.

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In 1909, the German neurologist Bálint described patients with a striking set of visuospatial defects (Bálint, 1909), which became known as Bálint syndrome; these deficits manifest after development of multiple cerebrovascular lesions mainly in the bilateral parietal lobes. The characteristic Bálint syndrome defects are psychic paralysis of gaze, spatial disorder of attention, and optic ataxia. Psychic paralysis of gaze is an inability to voluntarily shift one's gaze to an object of interest despite unrestricted ocular movement. Spatial disorder of attention, also known as dorsal simultanagnosia (Luria, 1958; Rizzo & Vecera, 2002), is an inability to perceive several items in a visual scene at the same time. Optic ataxia is difficulty accurately reaching for an object under visual guidance despite having normal limb strength to do so. Given the substantial effect on visuospatial function associated with Bálint syndrome, affected individuals might be expected to have visuospatial working memory deficits (Rizzo & Vecera, 2002). Regarding the relationship between visuospatial working memory and visuospatial function, Malhotra et al. 2005 found that severity of left neglect correlated with visuospatial working memory capacity in unilateral neglect. In addition, although right-parietal-cortex activity has often been associated with visuospatial working memory (Malhotra, Coulthard, & Husain, 2009; Malhotra et al., 2005; Pisella, Berberovic, & Mattingley, 2004; Pisella et al., 2011; Prime, Vesia, & Crawford, 2011; Russell et al., 2010), imaging studies have also indicated bilateral parietal-cortex involvement in visuospatial working memory (Oliveri et al., 2001; Postle & D'Esposito, 1999; Postle, Stern, Rosen, & Corkin, 2000).

Bálint syndrome patients were first described over a century ago. However, only a small number of Bálint patients have been examined for possible visuospatial working memory impairment (Pisella, Biotti, & Vighetto, 2015; Valenza, Murray, Ptak, & Vuilleumier, 2004). Valenza et al. 2004 found that the ability of a Bálint patient to form stable representations of visuospatial locations after a short delay was greatly impaired as the patient had very poor accuracy in location-matching performance compared with healthy subjects, suggesting of visuospatial working memory impairment. Pisella et al. 2015 showed that dorsal simultanagnosia in patients with degenerative bilateral posterior cortical atrophy could be observed with or without revisiting behaviour, an expression of visuospatial working memory across saccades. These results prompted us to explore this topic by studying a group of patients with non-degenerative Bálint syndrome, who have more focal damage and more limited neuropsychological dysfunctions compared with those with a degenerative condition.

We hypothesised that Bálint syndrome patients would have poorer visuospatial working memory than normal subjects or those with other types of brain damage. Accordingly, for this report we used variants of the Corsi block task (Corsi, 1972; Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000; Parmentier, 2011) and visuospatial-temporal integration with the shape-from-moving-dots (Stark, Coslett, & Saffran, 1996) to compare the visuospatial working memory of Bálint syndrome patients with those of healthy individuals and subjects with right-parietal damage.

2. Methods

2.1. *Participants*

Ethical aspects of this study were reviewed and approved by the Ashikaga Hospital Human Research Ethics Committee. This study was performed after obtaining informed consent from all subjects according to the Declaration of Helsinki. Bálint syndrome patients and right-parietal-damage controls were recruited from the Cognitive Function Clinics at the Ashikaga Red Cross and Edogawa Hospitals between August 2014 and December 2014. The right-parietal-damage group was included because many studies have shown that visuospatial working memory relies on right-parietal-cortex function (Malhotra et al., 2005, 2009; Pisella et al., 2004, 2011; Prime et al., 2011; Russell et al., 2010). To be included in the study, the participants met these eight criteria: (1) were native Japanese with ≥12 years of education, (2) had no degenerative disorders, (3) had no neurological or psychiatric disorders prior to their brain damage, (4) were ≥6 months post-onset of their disorder, (5) had >20/25 vision, (6) had no ocular palsy, (7) were able to perform activities of daily living, including feeding themselves and the routine use of the toilet, (8) were able to understand and follow task instructions.

In addition, the Bálint syndrome patients met the following two criteria, they: (1) had dorsal simultanagnosia at the time of our examination, which is considered the hallmark of Bálint syndrome (Rizzo and Vecera, 2002) and (2) had presented with at least two of the following three signs after they had become medically stable: psychic paralysis of gaze, dorsal simultanagnosia, and optic ataxia. For assessment of dorsal simultanagnosia, we followed the method of Rizzo and Vecera (2002), for which a patient must have met all of the following criteria. (1) The patient complained that stationary objects in the visual environment would disappear from direct view. (2) The patient reported intermittent or fragmentary perception of the visual environment. (3) The patient was unable to make visual sense of the complete Boston Cookie Theft picture (Goodglass & Kaplan, 1983). (4) The patient failed to properly count the number of dots in at least one of the three trials (3, 4, and 5 dots in descending order) in the visual perception test for agnosia (Japan Society for Higher Brain Function, 1998). For assessment of psychic paralysis of gaze and optic ataxia, we used the tests of Kas et al. (2011) as follows. The patient was seated in front of the examiner at a distance of 50 cm and asked to move his or her eyes towards a moving target, a 100-yen coin, after staring at the examiner's nose. The examiner moved the target through the four visual quadrants. If the patient failed to move his or her eyes in the direction of the coin in any of the four visual quadrants, he or she was diagnosed as having psychic paralysis of gaze. For assessment of optic ataxia, the patient, seated in front of the examiner at a distance of 50 cm, was asked first to stare at the examiner's nose and then to use a designated hand (left or right) to touch the target, a 100-yen coin. The examiner placed the target one at a time in each of the four visual quadrants. Even if a patient could move his or her eyes towards the target but could not accurately reach for the target with either hand on the first attempt in all of the four visual quadrants, he or she was diagnosed as having optic ataxia.

Among the 202 outpatients examined, 104 who were at the Ashikaga Red Cross Hospital clinic ($n = 83$) or at the Edogawa Hospital clinic ($n = 21$) met the basic inclusion criteria. Among those patients, six also met the inclusion criteria for Bálint syndrome, with four being from the Ashikaga Red Cross Hospital, and two from the Edogawa Hospital. The aetiology of Bálint syndrome was cerebrovascular disease for five patients and traumatic brain injury for the sixth patient. Patients 1–3 (Table 1) displayed all three symptoms at the time that they were considered to be medically stable (6 months post-brain damage). Patient 1 had all three symptoms at the time of our examination, whereas psychic paralysis of gaze in patients 2 and 3 had gradually resolved within 1 year after brain damage. These two patients had only dorsal simultanagnosia and optic ataxia at the time of our examination. Patients 4–6 had only dorsal simultanagnosia and optic ataxia at the time that they were considered to be medically stable (6 months post-brain damage). Their symptoms thereafter improved within 1 year such that they had only dorsal simultanagnosia at the time of our examination. A detailed description of these patients is provided in Sunagawa, Nakagawa, and Funayama (2015).

The right-parietal-damage group was recruited from the aforementioned 202 patients. For inclusion in the study, these patients needed to have obvious right-parietal lesions as demonstrated by their most recent computed tomography or magnetic resonance imaging (MRI) results. Although 17 patients met these criteria, one patient could not understand instructions because he had difficulty hearing, and another declined to participate in this study, so only 15 patients were included in the right-parietal-damage group. Among the 15 patients, 14 were from the Ashikaga Red Cross Hospital clinic, and one was from the Edogawa Hospital clinic. The aetiology was cerebrovascular disease for 12 patients, traumatic brain injury for two patients, and brain tumour for one patient. Nine patients had left-sided unilateral spatial neglect at the time when they were considered to be medically stable. However, most showed improvement within 1 year so that only one patient had mild neglect at the time of our examination.

Twenty-six healthy individuals without brain injury or psychiatric disease were recruited from the staff and family members of the patients at the Ashikaga Red Cross Hospital to form the healthy control group. The study took place in the Ashikaga Red Cross and Edogawa Hospital clinics.

2.2. Demographics and basic neuropsychological assessments

The demographic factors investigated were age, gender, and level of education. The number of years post-onset for the Bálint syndrome and the right-parietal-damage patients was also recorded. Patients in these two groups completed a battery of standardised neuropsychological tests that covered basic cognitive function, language, episodic memory, and visuospatial function. We measured visuospatial function because visuospatial working memory is naturally related to visuospatial function. In addition, because visuospatial working memory has been postulated to interact with episodic long-term memory, language, reasoning, comprehension, and learning (Baddely, 2010), we also measured basic cognitive function, linguistic function, and episodic memory function. Basic cognitive function was evaluated using the Revised Hasegawa Dementia Rating Scale (HDS-R) (Katoh et al., 1991), which is similar to the Mini-Mental State Examination and is most frequently used for basic cognitive function in Japan. The HDS-R includes items that assess orientation, memory, repetition, backward digit span, calculation, and category fluency. The maximum number of possible points attainable for the HDS-R is 30, as it is for the Mini-Mental State Examination. The passing cut-off point for Mini-Mental State Examination is 23, whereas that for the HDS-R is 20. For linguistic function, the Japanese version of the Wechsler Adult Intelligence Scale (Fujii, 2006) was used to test the subjects' verbal intelligence quotient (VIQ). The Japanese version of the Rivermead Behavioural Memory Test (RBMT) (Watanuki, Hara, Miyamori, & Etoh, 2002) was

Table 1 – Demographics and neuropsychological data.

Participants or group	Age, yr/Gender	Education, yr	Years post-onset	Digit span	HDS-R[a]	VIQ[b]	PIQ[b]	RBMT	TMT-A (s)[c]
Participant									
Bálint 1	70/F	16	11	3	13	83	46	1	DNF
Bálint 2	67/F	12	8	5	27	100	45	2	DNF
Bálint 3	63/F	12	3	5	11	64	45	3	DNF
Bálint 4	57/M	12	1	4	17	60	48	3	DNF
Bálint 5	57/M	16	7	4	29	111	63	1	245
Bálint 6	65/F	12	28	5	26	95	73	1	318
Bálint group	63.1 ± 4.8	13.3 ± 1.9	9.7 ± 8.8	4.3 ± 0.7	20.5 ± 7.1	85.5 ± 18.6	53.3 ± 10.8	1.8 ± 0.9	493.8 ± 151.6
Right parietal	55.7 ± 11.0 M12, F3	12.7 ± 1.4	7.6 ± 7.3	6.1 ± 1.6	24.2 ± 4.6	84.1 ± 13.3	68.0 ± 12.6	3.3 ± 2.0	247.3 ± 128.9
Healthy control	61.0 ± 5.6 M13, F13	12.8 ± 1.6	–	NA	NA	NA	NA	NA	NA

Note. Maximum time on the TMT-A was 600 sec; participants not finishing with that time limit are indicated by DNF. -, not applicable; DNF, did not finish; F, female; M, male; HDS-R, Hasegawa Dementia Rating Scale Revised score; NA, not assessed; PIQ, performance intelligence quotient; RBMT, Rivermead Behavioural Memory Test score; TMT-A, Trail Making Test A score; VIQ, verbal intelligence quotient.

[a] Cutoff, 20.

[b] Range, 70–130.

[c] Average for 60 sec, 157.6.

employed to assess episodic memory function. Of the 11 RBMT subtests, two subtests, i.e., recalling a short route and remembering an errand run, were expected to be impossible for the Bálint syndrome patients owing to their severe visuospatial deficits. Therefore, we used only the other nine RBMT subtests to assess participants' episodic memory function, making for a maximum screening score of nine. Visuospatial function and performance intelligence quotient (PIQ) of the subjects were evaluated using the Japanese version of the Trail Making Test A (TMT-A) (Kashima, Handa, & Katoh, 1986) and the Japanese version of the Wechsler Adult Intelligence Scale (Fujii, 2006), respectively. Performance on these tests was expected to be severely impaired for Bálint syndrome patients owing to their visuospatial deficits. In the TMT-A test, participants are instructed to connect a set of 25 numbers written on paper to assess simple visuospatial function, and the Wechsler Adult Intelligence Scale was employed to measure more complex visuospatial functions, such as block design. The time limit for the TMT-A was 600 sec. If the subject had not completed the test in this time, the trial was terminated, and a value of 600 sec was used for statistical analysis. To assess phonological working memory along with visuospatial working memory, forward digit span from the Japaneses version of the Wechsler Memory Scale-Revised (Sugishita, 2001) was evaluated.

2.3. *Neuroanatomical analysis*

As is often found for patients with watershed infarctions (Bohdiewicz & Juni, 1994; Sullivan, Villanueva-Meyer, Liu, Giombetti, & Mena, 1991), Bálint syndrome patient 3 who had a watershed infarction caused by hypotension did not present with lesions on MRI or computed tomography, whereas a single-photon emission computed tomography of her brain demonstrated a remarkable hypoperfusion in her bilateral parieto-occipital lobes. Except for this patient, lesions of the other five Bálint syndrome patients overlapped. The lesions of the 15 right-parietal-damage group also overlapped.

Images of the overlapped lesions from the most recent clinical structural brain scans of the Bálint syndrome patients were generated using MRIcro software (http://www.mccauslandcenter.sc.edu/mricrogl/; McCausland Center for Brain Imaging, Columbia, SC). A speech therapist (Y. N.) who had 3 years of experience with this method at the time of the study performed the analysis without knowing how the patients had performed on the visuospatial working memory tasks and their neuropsychological assessments. This method is essentially a direct-to-digital variant of template-based spatial normalisation that has been the standard approach for lesion studies for a group of patients and remains the gold standard for delineation of chronic brain lesions with intraclass correlation coefficients of .86–.95 (Wilke, de Haan, Juenger, & Karnath, 2011). Individual lesions were traced from the most recent clinical MRIs of the patients. The method used to transpose lesions was as follows. All major sulci in the lesions were identified. Each lesion boundary was traced and manually transferred onto the template brain taking into account the relation of the lesion boundary to the identified sulci. After transferring all lesion images, the regions of interest were overlapped to explore their mutual involvement on a voxel-by-voxel basis using the MRIcro regions-of-interest menu commands.

Fig. 1A shows the image of the overlapped lesions for the five Bálint syndrome patients. The lesions mainly overlap in the bilateral parieto-occipital lobes, which is a finding comparable with those reported previously (Bálint, 1909; Rizzo &Vecera, 2002). Fig. 1B shows the image of the overlapped lesions for the 15 right-parietal-damage patients.

2.4. *Experiments assessing visuospatial working memory*

Visuospatial working memory capacity has been measured using variations of the Corsi block task (Corsi, 1972; Kessels et al., 2000; Parmentier, 2011) in which participants encode and recall the order of presentation of spatial locations marked in sequence. Recently, computerized variants of this task have been developed, namely, delayed visuospatial matching tasks (Carlesimo, Perri, Turriziani, Tomaiuolo, & Caltagirone, 2001; Finke, Bublak, & Zihl, 2006; Malhotra et al., 2005; Oliveri et al., 2001; Pisella et al., 2004; Postle & D'Esposito, 1999; Postle et al., 2000; Valenza et al., 2004). Participants are required to verbally answer questions concerning visuospatial locations without involving upper-limb movement. The basic task for these tests is to visually recall spatial locations that were presented several seconds earlier. We employed the simplest version of these tests given the severe visuospatial deficits associated with Bálint syndrome. Participants were required to observe a sequence of probe locations and to make a choice about whether the probe location of the response phase had been the same as that of the study phase. However, before investigating visuospatial working memory, it was necessary to assess how they inputted visuospatial information. As is often the case with severe Bálint syndrome patients, they sometimes are unable to perceive even one or two objects at a time. We therefore first assessed if the participants could perceive several objects at a time and correctly judge the positional relationship of those objects.

2.4.1. *Experiment 1: judgment of positional relationships*

2.4.1.1. Judgment of positional relationships of two probes. We developed a task to judge the positional relationships of two circles using PowerPoint 2010. Although this task is novel, its concept is based on those investigated in visual disorientation syndrome (Holmes, 1918; Holmes & Horrax, 1919), an analogue of Bálint syndrome, in which difficulty judging positional relationships between objects is one of the main symptoms. Two circles, one blue and one red, each with a 2.5-cm diameter, were displayed on a computer screen (Toshiba Dynabook T5 53/67JB; 34 × 20 cm) and viewed by the subjects from a distance of 50 cm. The centres of the circles were separated by at least 2 cm. As the height of the screen was 20 cm, nine positions were marked 2-cm apart on the vertical meridian, which circumvented a potential impact of left unilateral neglect by the subjects. The two circles were presented together in two of the nine positions on the screen. Participants were asked if the red circle was above or below the blue one. A total of 30 trials were performed for each participant, with the red circle above the blue one in 50% of the trials. We

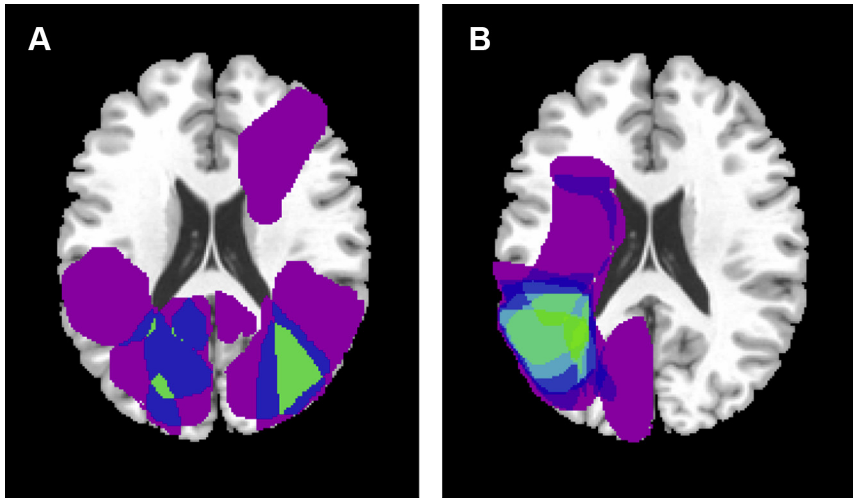

Fig. 1 – A Overlap of Bálint syndrome patient lesions. Green represents regions of maximum overlap and purple represents regions of minimum overlap. The affected areas mainly overlap in the bilateral parieto-occipital lobes. B Overlap of right-parietal-damage group lesions. Green represents regions of maximum overlap and purple represents regions of minimum overlap. The affected areas mainly overlap in the right parietal lobe.

set a time limit for this task. If the participants had not start providing an answer within 3 sec, the trial was counted as an incorrect answer. Before starting the experiment, participants had three practice trials. If a participant answered incorrectly during one of the 30 trials, he or she was regarded as having difficulty judging the positional relationship between two objects.

2.4.1.2. Judgment of positional relationships among three probes. Next, a judgment task concerning the positional relationships among three circles (one coloured blue, one red, and one yellow) with the same vertical separation was performed. The trial was similar to the aforementioned task, and participants were asked to judge the position of the yellow circle, i.e., upper, middle, or lower. The yellow circle was in the top position in 10 trials, the middle position in 10 trials, and the bottom in 10 trials. Chance performance was 1/3 in this three-alternative forced-choice task. The time limit for judgment of positional relation was 3 sec. Before starting the experiment, participants had three practice trials. If a participant answered incorrectly during one of the 30 trials, he or she was regarded as having difficulty judging the positional relationship among three objects.

2.4.2. *Experiment 2: visuospatial working memory*

2.4.2.1. Visuospatial working memory for one location. A task for visuospatial working memory (Fig. 2), developed using PowerPoint 2010, was presented on the same computer screen as for Experiment 1 and was viewed from a distance of 50 cm. Much of the configuration followed that for Malhotra's task (Malhotra et al., 2005), which targeted unilateral spatial neglect. However, given the severe visuospatial deficits of Bálint syndrome patients, we made this task as simple as possible. First (study phase), a blue circle, 2.5 cm in diameter, was displayed for 2 sec in one of the nine locations used for Experiment 1. (Malhotra et al., 2005 used a circle of 1.5 cm in diameter, which was displayed for 1 sec in one of the ten locations.) Then, after removing the blue circle and a 1-sec delay, a new blue circle was shown in any one of the nine locations (response phase). The display of each circle was accompanied by a beeping sound. For half of the trials, the locations of the two circles were the same. Participants were instructed to say "same" when the circles were in the same place and "different" when they were not. There was no limit on the response time. Before starting an experiment, each participant was given demonstrations with the circles in the same and different locations. Thirty trials were performed per participant. The maximum score was 30.

If a participant performed well when tested using the positional relationship between two circles presented at the same time (Experiment 1) but poorly on this experiment, we considered the participant to have poor visuospatial working

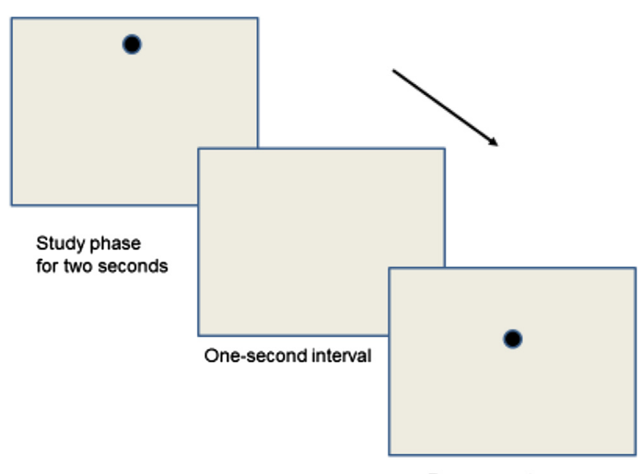

Fig. 2 – Visuospatial working memory for one location. Participants were asked whether the locations of the circles were in the same place, or not, in the study and response phases.

memory because, although the participant could perceive and positionally relate two objects at the same time, the participant could not keep the location of the first circle in mind for even a few seconds.

2.4.2.2. Visuospatial working memory for a sequence of two locations. The second task was more difficult than the first as it required each participant to identify an object located sequentially at two different places during the study phase. First, for the study phase, a blue circle was presented for 2 sec in one of the nine aforementioned locations, followed immediately by a second blue circle for 2 sec at one of the other eight locations (the first circle having been removed). Each circle presentation was accompanied by a beeping sound. After presentation of the first and second circles, there was a 1-sec delay after which a participant was shown another blue circle (response phase) in any one of the nine locations. Thirty trials were performed per participant. The participants were then asked to state "same" or "different" if the location of the third circle was the same as one of the two circles or different from both of the circles. For 10 trials, the position of the third circle was the same as that of the first, and for five trials its position was the same as that of the second. For 15 trials, the position of the third circle was different from both the first and second circles. The participants did not have to tell the position of the first or second circle when stating same or different. There was no limit on the time the participant had to answer during the response phase. Before starting the experiment, participants were given three demonstrations: two correct trials, congruent with either the first circle or the second circle, and an incorrect trial. The maximum number of possible correct answers was 30. If a participant had acceptable results on the judgment of positional relationship between two or three circles presented at the same time (Experiment 1) but poor results for this experiment, we considered that they had poor visuospatial working memory. Although the participant could perceive and positionally relate two or three objects simultaneously (Experiment 1), the participant could not keep the locations of the two probes in mind for even a few seconds. (Whereas Malhotra et al. 2005 covered visuospatial working memory abilities for sequence lengths of up to five locations, we finished this visuospatial working memory task at sequence lengths of two locations considering the severe visuospatial deficits of Bálint syndrome patients.)

2.4.3. *Experiment 3: visuospatial-temporal integration with shape-from-moving-dots*

Experiment 2 focused on visuospatial working memory as a test of short-term recall, which is an important component of visuospatial working memory. However, short-term memory is a rather passive function, and as we were also interested in working memory, we wanted to investigate the more active visuospatial working memory. To this end, we assessed visuospatial working memory capacity for visuospatial representation using a shape-from-moving-dots task, during which participants were asked to name shapes consisting of consecutively moving dots (Fig. 3). We assumed that a rapidly decaying retinotopic display would not be sufficient to perform the task and that maintenance of information at the level of the visuospatial working memory would be required. The basic configuration followed that of Stark et al. (1996), in which they used to measure visuospatial representation ability—an analogue of visuospatial working memory—for a patient with posterior cortical atrophy. This task was developed using PowerPoint 2010 and was presented on the same computer screen as used for Experiments 1 and 2. The screen was again viewed from a distance of 50 cm. We presented three simple geometrical objects (triangle, square, and cross) and seven capital letters (E, F, H, I, L, T, and Z as did Stark and colleagues) that were formed by sequentially appearing and then disappearing dots .2 cm in diameter. The dots were displayed one at a time so that the dots needed to be imaginarily integrated across space and time to generate a complete object, or, in other words, "imaginary writing" the letter or object on the screen over time. Each object or letter comprised of 18–39 dots as was true for Stark's task. Each dot was displayed for 1 sec, which was a longer time than used in Stark's task but was chosen because the Bálint syndrome patients might have difficulties tracking the dots. There was no delay before displaying the next dot as was also true for Stark's task. The direction of motion was restricted to the horizontal and vertical axes, and along the 45° diagonals. The participants were notified that the ten shapes would each be a geometrical object or a capital letter of the English alphabet. Then, they were instructed to name the geometrical object or letter after each full display. There was no time limit on the response phase. The maximum number of correct answers was 10.

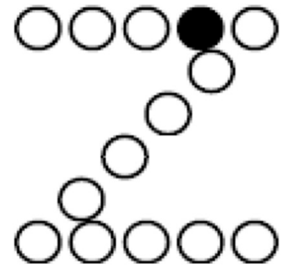

Fig. 3 – Visuospatial-temporal integration for shape-from-moving-dots. Each dot was presented for 1 sec with no interval between presentations, i.e., the dots were displayed one at a time, which forced the subject to integrate them across space and time to generate a complete object.

2.5. *Statistical analysis*

The performances of the Bálint syndrome group were compared with those of the right-parietal-damage group and the healthy group. Excel 2010 with add-on Statcel 3 (OMS Ltd., Tokyo) was used for all statistical analyses. Significance was set at $p < .05$, two tailed. Age and education were assigned unequal variance and were compared across the three groups using the Kruskal–Wallis test. Gender distribution was compared across the three groups using Fisher's exact test. Neuropsychological data (HDS-R, VIQ, PIQ, RBMT, and TMT-A) and years post-onset for the Bálint syndrome group were nonparametric variables and were compared across the Bálint syndrome group and the right-parietal-damage group using the Mann–Whitney U test. For the experimental trials, visuospatial working memory and visuospatial-temporal integration were each compared across the three groups using the Kruskal–Wallis test because the results of Bálint syndrome group were nonparametric. Post-hoc pairwise comparisons were made using the Steel–Dwass test.

A second analysis considered only the results for the mild Bálint syndrome patients defined as those who had scored 100% on the judgment of positional relationship test for two locations. The demographic factors, neuropsychological data, and the results of the experimental trials for this group were compared with those of the two control groups.

Lastly, to account for potential confounders, e.g., the influence of episodic memory deficits on visuospatial working memory, a multiple linear regression was performed for the data of the Bálint syndrome and right-parietal-damage group. Each explanatory variable, i.e., the neuropsychological (HDS-R for basic cognitive function, VIQ for verbal ability, PIQ for performance ability, RBMT for episodic-memory function, TMT-A for visuospatial function) and demographic data (age, gender, education, and years post-onset) was subjected to a multiple linear regression for each experimental result.

3. Results

3.1. *Demographic factors and neuropsychological data*

Table 1 shows the basic demographic factors (age, gender, education level, and years post-onset) and the neuropsychological test scores for the six Bálint syndrome patients and the average for each group. The Bálint syndrome group and the two control groups did not differ with respect to age (Kruskal–Wallis test, $p = .17$), education (Kruskal–Wallis test, $p = .72$), or gender distribution (Fisher's exact test, $p = .10$). The scores for HDS-R (Mann–Whitney's U test, $p = .39$), VIQ (Mann–Whitney's U test, $p = .76$), and RBMT (Mann–Whitney's U test, $p = .11$) and the years post-onset (Mann–Whitney's U test, $p = .67$) were similar for the mild Bálint syndrome group and the right-parietal-damage group. However, the scores for the two tests that involved visuospatial function (PIQ and TMT-A) were less for the Bálint syndrome group than for the right-parietal-damage group (Mann–Whitney's U test, $p < .05$ for both tests). Four of the Bálint syndrome patients did not finish the TMT-A within the 600-sec limit.

3.2. *Experiment 1: judgment of positional relationships*

Fig. 4 shows the percentages of correct answers for the judgment of positional relationship test. Both control groups had perfect scores when two or three probes were displayed. In contrast, patients 1 and 2 with severe Bálint syndrome could not judge the positional relationships for two probes (0 and 19 out of 30 trials for patient 1 and patient 2, respectively) and patients 1–4 could not judge the positional relationships for three probes (0, 1, 2, and 23 out of 30 trials for patient 1, 2, 3, and 4, respectively). Conversely, patients 3–6 could determine the positional relationship between two probes. These patients formed the mild Bálint syndrome group.

3.3. *Experiment 2: visuospatial working memory*

3.3.1. *Visuospatial working memory for one location*

Fig. 4 shows the percentages of correct answers for all three groups. The scores differed across the three groups (Kruskal–Wallis test, $p < .01$). Post-hoc comparisons showed that the Bálint syndrome group performed worse than both control groups (Steel–Dwass test, $p < .01$ for both comparisons). The performances of the two control groups did not differ significantly (Steel–Dwass test, $p > .05$).

Most of the comparisons were similar after removing the results for patients 1 and 2 with severe Bálint syndrome from the analysis. Age (Kruskal–Wallis test, $p = .27$), education (Kruskal–Wallis test, $p = .96$), and gender distribution (Fisher's exact test, $p = .12$) did not significantly differ for patients with mild Bálint syndrome and those in the control groups. The HDS-R scores (Mann–Whitney's U test, $p = .45$), VIQs (Mann–Whitney's U test, $p = 1.0$), RBMTs (Mann–Whitney's U test, $p = .26$), and years post-onset (Mann–Whitney's U test, $p = .88$) also were not significantly different for mild Bálint syndrome group and right-parietal-damage group. For the PIQ and TMT-A tests, which involved visuospatial function, although the PIQ scores did not significantly differ for the mild Bálint syndrome group and the right-parietal-damage group (Mann–Whitney's U test, $p = .21$), the mild Bálint syndrome group had a tendency to have poorer TMT-A scores compared with those of the right-parietal-damage group (Mann–Whitney's U test, $p = .07$). As for visuospatial working memory of one location, the scores differed across the three groups (Kruskal–Wallis test, $p < .01$). Post-hoc comparisons showed that the mild Bálint syndrome group performed worse than either control group (Steel–Dwass test, $p < .01$ for both comparisons).

3.3.2. *Visuospatial working memory of two locations*

Fig. 4 shows the percentages of correct answers for visuospatial working memory of two locations for all three groups. The scores differed across the three groups (Kruskal–Wallis test, $p < .01$). Post-hoc comparisons show that the Bálint syndrome group performed worse than did the two control groups (Steel–Dwass test, $p < .01$ for both comparisons). The right-parietal-damage group also performed worse than the healthy group (Steel–Dwass test, $p < .05$).

The results were similar when patients 1 and 2 with severe Bálint syndrome were excluded. Even after eliminating the results for patients 1 and 2, and including only those for the mild Bálint syndrome patients, the scores differed across the three groups (Kruskal–Wallis test, $p < .01$). Post-hoc comparisons showed that the mild Bálint syndrome group performed worse than the healthy group (Steel–Dwass test, $p < .01$).

The results were also similar when the four Bálint syndrome patients who could not judge the positional relationship among three probes (patient 1–4) were excluded from the comparisons. Although the average scores for the right-parietal-damage and healthy groups were 22.2 ± 3.7 and 25.5 ± 3.7, respectively, the scores for patients 5 and 6 with the mildest form of Bálint syndrome who performed perfectly on judgment of positional relationships among three probes were 16 and 17, respectively. The performances of these two Bálint syndrome patients were

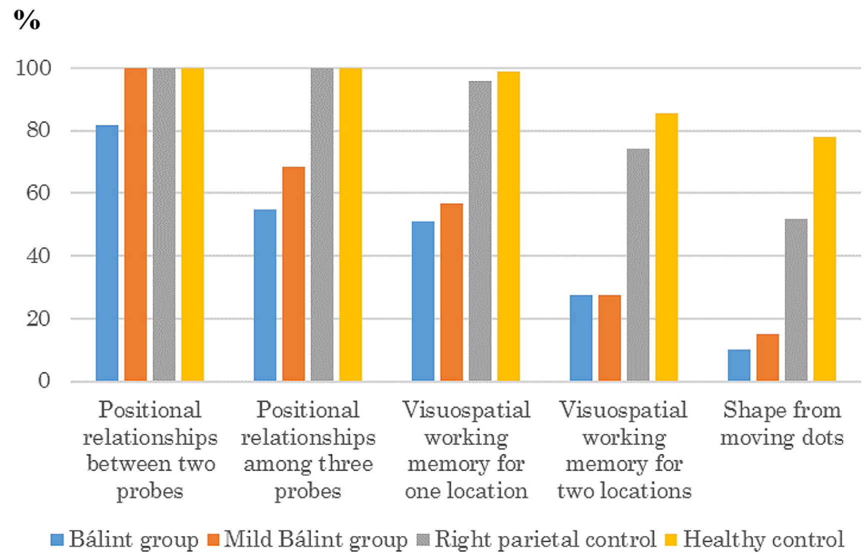

Fig. 4 – Percentages of correct answers for judgment of positional relationship and visuospatial working memory trials. Mild Bálint group refers to patients with Bálint syndrome who scored 100% on the judgment of positional relationship between two probes trial.

<8% and <1% in comparison with the percentiles for the right-parietal-damage and the healthy groups, respectively.

3.4. *Experiment 3: visuospatial temporal integration with shape-from-moving-dots*

Fig. 4 shows the percentages of correct answers for all three groups. The scores differed across the three groups (Kruskal–Wallis test, $p < .01$). Post-hoc comparisons showed that the Bálint syndrome group performed worse than the other two groups (Steel–Dwass test, $p < .01$ for both comparisons). The right-parietal-damage group also performed worse than the healthy group (Steel–Dwass test, $p < .01$).

In summary, visuospatial working memory was severely impaired in Bálint syndrome patients compared with the subjects of the control groups. The difference remained when the comparisons were made between only the mild Bálint syndrome patients and the subjects in the other two groups.

3.5. *Multiple linear regression analysis*

The results for Experiments 2 and 3 were analysed using multiple linear regression. The multiple linear regressions indicate that the PIQ score, an index for visuospatial function, positively influenced the visuospatial working memory score for visuospatial-temporal integration of the shape-from-moving-dot trial after controlling for other variables ($p < .01$). Conversely, no other variables had a significant influence on any experimental result, suggesting that the other measured neuropsychological functions, e.g., basic cognitive function (HDS-R) and episodic memory function (RBMT), are unlikely to influence visuospatial working memory.

4. Discussion

This is the first report to compare visuospatial working memory of Bálint syndrome patients with that of right-parietal-damage patients. We found that Bálint syndrome patients have significantly more severe visuospatial working memory deficits. Although the delayed visuospatial matching tasks (Experiment 2) that we used were much simpler than those used previously (Carlesimo et al., 2001; Finke et al., 2006; Malhotra et al., 2005; Oliveri et al., 2001; Pisella et al., 2004; Postle & D'Esposito, 1999; Postle et al., 2000; Valenza et al., 2004), our Bálint syndrome patients still performed extremely poorly. In fact, they could not maintain a representation of visuospatial information for even a few seconds. This inability was unlikely to be resulted from an episodic memory deficit because their episodic memory deficits were unrelated to their visuospatial working memories according to multiple linear regression analysis.

Increasing evidence suggests that visuospatial working memory relies on right-parietal-cortex activity (Malhotra et al., 2005, 2009; Pisella et al., 2004, 2011; Prime et al., 2011; Russell et al., 2010), which is compatible with our results, as the right-parietal-damage group performed worse than did the healthy group for the visuospatial working memory task for two locations and the visuospatial temporal integration task. Notably, we found that the Bálint syndrome patients had more severe visuospatial working memory deficits than did the right-parietal-damage group, which might be related to bilateral brain damage as opposed to unilateral damage. Although right-parietal-cortex activity has often been associated with visuospatial working memory (Malhotra et al., 2005, 2009; Pisella et al., 2004, 2011; Prime et al., 2011; Russell et al., 2010), imaging studies have also indicated bilateral parietal-cortex involvement (Oliveri et al., 2001; Postle & D'Esposito, 1999; Postle et al., 2000). Using functional MRI-type neuroimaging, Postle and colleagues showed that bilateral parieto-occipital cortex activation occurs during a visuospatial working memory task (Postle & D'Esposito, 1999); later, this group also demonstrated that bilateral parietal-cortex activation is associated with visuospatial working memory (Postle et al., 2000). Similarly, using transcranial magnetic stimulation, Oliveri and colleagues showed that bilateral parietal transcranial magnetic stimulation selectively increases reaction times during a visuospatial working memory task (Oliveri et al., 2001). Another possibility might be qualitative difference between Bálint syndrome and visuospatial deficits of the right inferior parietal cortex damage. As shown in Fig. 4, there were large differences in visuospatial working memory performance between the mild Bálint syndrome group and the right-parietal-damage group when assessed with higher memory load of two locations or many dots. It has been recently suggested that the bilateral superior parietal lobule creates a reduction of the orienting of attention toward peripheral locations in the contralateral visual field (Gillebert et al., 2011) which impairs the input process of visuospatial information and might thus decrease the performance in visuospatial working memory tasks, whereas that the right inferior parietal cortex is specific to visuospatial working memory across saccades (Pisella et al., 2015). In fact, the lesions for the Bálint syndrome group overlap in the superior and inferior parietal lobules, whereas those for the right-parietal-damage group overlap mainly in the inferior parietal lobule (Fig. 1). Although we controlled the input process of visuospatial information by using the mild Bálint syndrome patients who were able to judge positional relationships between two objects, their potential reduction of the attentional field for more than two objects might have led to extremely poor performance in the visuospatial working memory tasks with higher memory load.

Poor visuospatial working memory associated with Bálint syndrome would at least partly explain the visuospatial difficulties displayed by Bálint syndrome patients. These difficulties, e.g., bumping into objects or people and being lost in their own homes, might reflect visuospatial working memory deficits, because, as we have now shown, they are unable to maintain the locations of objects that they saw just a few seconds earlier. In fact, patient 5 with mild Bálint syndrome, who sometimes hit her head against the table when picking up an object such as a spoon from under the table, said that the location of the table in relation to the object immediately disappeared after she saw the object needing to be picked up (Sunagawa et al., 2015).

Our study has several limitations that should be considered when interpreting the results. First, the number of Bálint syndrome patients was small. However, Bálint syndrome is rarely found in patients with brain damage, which precludes studying a large cohort, and thus our study likely represents the best possible assessment of a cohort of Bálint patients. Second, owing to the small numbers of participants with brain damage (Bálint patients and the right-parietal-damage group), a meaningful statistical confidence level for the multiple linear regression analyses may not have been achieved. Third, the visuospatial working memory tasks that we employed did not address the relationship between the observer and the object (egocentric spatial processing) (Aguirre & D'Esposite, 1999) but only the positional relation between objects (allocentric spatial processing). Difficulties associated with visuospatial working memory for Bálint syndrome patients might be related more to egocentric spatial processing than to allocentric spatial processing. Based on our clinical observations, however, most Bálint syndrome patients have impairments of both egocentric and allocentric spatial processing. Finally, we did not perform the horizontal version of our experiments. However, results for the horizontal version by the right-parietal-damage group would have been more difficult to analyse owing to potential left-sided unilateral spatial neglect.

Despite these limitations, our study sheds light on the daily living difficulties encountered by Bálint syndrome patients owing to their extremely poor visuospatial working memory.

5. Conclusions

Visuospatial working memory was severely impaired in Bálint syndrome patients compared with the subjects in the control groups. The differences remained when only data for patients with a mild form of Bálint syndrome were included. This deficit might influence their inability to properly execute movements associated with daily living.

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Competing interests

None.

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