Quantifying egocentric spatial neglect with cancellation tasks: a theoretical validation

Hanne Huygelier[1] and Celine R. Gillebert*[1,2]

[1]Department of Brain and Cognition, KU Leuven, Leuven, Belgium

[2]Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom

*Corresponding author Céline R. Gillebert, Tiensestraat 102 Leuven 3000, Belgium (e-mail: celine.gillebert@kuleuven.be).

Acknowledgements

This work has been funded by a personal fellowship awarded to Hanne Huygelier by the Research Foundation Flanders (1171717N) and a grant awarded to Céline R. Gillebert (G072517N). We would like to thank Pieter Moors, Johan Wagemans, Brenda Schraepen, Lulu Wang and Margaret Moore for their feedback on an earlier version of this manuscript.

Abstract

Spatial neglect is characterized by a spatial bias in responses to stimuli. The disorder is often assessed with a cancellation task, where several measures can be used to quantify the spatial bias of cancellation responses (e.g. the difference between cancellations on the left and right side, the average location of cancelled targets, and the total number of omissions). Typically, measures of cancellation performance are validated by studying the correlation with measures derived from other tasks to assess neglect (e.g. the directional bisection error derived from performance on the line bisection task). However, the foundation of cancellation performance measures is often more intuitive than theoretical. For instance, it is assumed that measures of cancellation performance isolate the spatial (e.g. the ipsilesional preference typical of spatial neglect) from the non-spatial (e.g. deficits in working memory or sustained attention) sources of error, but this assumption has not been tested yet. Here we formulated a simple model with conceptually meaningful parameters to predict cancellation performance. Our model parameterizes the spatial and non-spatial components of cancellation responses. This model allowed us to study the construct representation of commonly used measures of spatial neglect through the use of Monte Carlo simulations. The results showed that most of the cancellation performance measures are also dependent on non-spatial error sources. The results deepen our understanding of the construct representation of cancellation performance measures, while also having implications for studies focused on the relationship between the spatial and non-spatial attention deficits in spatial neglect.

Introduction

Egocentric visuospatial neglect refers to a reduced ability to orient or respond to the side of space that is located contralateral to the damaged hemisphere (Heilman, Bowers, Valenstein, & Watson, 1987). Although many studies on spatial neglect are focused on the egocentric symptoms for the horizontal dimension, it is also known that the spatial bias can extend into the ipsilesional side of space (Rorden & Karnath, 2010) and is not necessarily restricted to the horizontal dimension (Cazzoli, Nyffeler, Hess, & Müri, 2011; Halligan & Marshall, 1989; Mark & Monson, 1997; Rapcsak, Cimino, & Heilman, 1988).

The reduced awareness for or responsiveness towards contralesional events can be explained by a biased spatial attention, in which patients with spatial neglect preferentially orient their attention towards the ipsilesional side of space (Bartolomeo, Thiebaut de Schotten, & Chica, 2012; Corbetta & Shulman, 2011). It has also been suggested that the spatial asymmetry can be explained by a deviated representation of egocentric space (Bisiach, Luzzatti, & Perani, 1979; Karnath, 1997; Wansard, Meulemans, & Geurten, 2016), or by a combination of a biased attentional priority map and a spatial remapping deficit (Pisella & Mattingley, 2004; Vandenberghe & Gillebert, 2009). Regardless of the precise mechanisms underlying spatial neglect, there is general consensus that spatial neglect is characterized by a spatial bias in orienting and responding to stimuli at the behavioral level. In addition, it has been suggested that the spatial symptoms are accompanied by non-spatial deficits, such as sustained attention and working memory deficits or a reduction of overall attentional capacity (Husain & Rorden, 2003; Pisella & Mattingley, 2004). Although non-spatial deficits in spatial neglect are an important component of the syndrome, the diagnosis of spatial neglect is primarily based on identifying a spatial bias in responses to peripheral stimuli. The spatial bias is often measured with a cancellation or line bisection task, with the cancellation task being the most popular tool (Bowen, McKenna, & Tallis, 1999).

In a cancellation task, the patient is presented with an array of stimuli and asked to mark certain stimuli (targets) while ignoring other stimuli (distractors). There are several cancellation tasks available that vary in the number of targets, the number of distractors and the type of stimuli in the array (see Table 1 for some examples). In addition to the numerous cancellation tasks, countless summary statistics have been used to quantify cancellation performance (Table 1). Simple cancellation performance measures are, for instance, the number of (contralesional) omissions and the difference between cancellations in the left and the right visual field (see Table 1). More complex cancellation performance measures have also been used, such as the center of cancellation (CoC) (Dalmaijer, Stigchel, Nijboer, Cornelissen, & Husain, 2014; Mark & Monson, 1997; Rorden & Karnath, 2010; Vaes et al., 2015) and estimating the extent to which performance depends on the target location using regression techniques (Chatterjee, Thompson, & Ricci, 1999). In addition to cancellation performance measures that aim to quantify the spatial bias, measures of search strategy have been devised, such as the starting point (Azouvi et al., 2006) or more complex ones (for an in-depth discussion, see Dalmaijer et al., 2014). However, given the requirement to register the order of the responses of the patient to quantify strategy, strategy measures are used less often as a basis for spatial neglect diagnosis than the cancellation performance measures presented in Table 1.

Table 1. Examples of different measures of cancellation performance.

Task	Summary Measure	Reference Example
Bells test	Number of contralesional omissions	(Gauthier et al., 1989)
	Difference between left and right omissions	(Azouvi et al., 2006; Rousseaux et al., 2001)
	Center of Cancellation	(Rorden & Karnath, 2010)
Letter Cancellation	Number of contralesional omissions	(Weintraub, 1985)
Oxford Cognitive Screen Hearts Cancellation	Difference between left and right cancellations	(Demeyere et al., 2015)
Diamond Cancellation	Center of Cancellation	(Vaes et al., 2015)
Line Cancellation	Total number of omissions	(Albert, 1973)
Star Cancellation	Number of contralesional omissions	(Bailey et al., 2004; Halligan, Cockburn, & Wilson, 1991)
	Contralesional cancellations divided by total cancellations	(Friedman, 1992)
	Difference between left and right cancellations divided by total number of cancellations	(McIntosh et al., 2000)

Spatial neglect can also be assessed with the line bisection task. In the line bisection task, the patient is asked to mark the midpoint of a line. The deviation away from the true midpoint, i.e. the *directional bisection error*, can then be used as an index of spatial bias. Importantly, several studies have shown that spatial biases on the line bisection and the cancellation task load onto two separate factors, suggesting that different cognitive processes may be involved in these tasks (Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010; Sperber & Karnath, 2016). These factor analytic studies prompted reinterpretation of the cognitive processes involved in completing the line bisection task, suggesting that line bisection performance reflects a more low-level perceptual component (associated with more posterior lesions) as compared to cancellation performance. However, a different method of quantifying the spatial bias on line bisection tasks (for details see McIntosh, Schindler, Birchall, & Milner, 2005) resulted in a better correspondence between the results of the line bisection and cancellation task (McIntosh, 2017). Construct validity may thus not only depend on the characteristics of the task, but also on the method used to quantify the performance on the task. McIntosh (2017) showed that the combination of two separate measures derived from the line bisection task, one tapping onto the spatial bias and one tapping onto a non-spatial component, had the strongest association with the total number of omissions on cancellation tasks. The latter suggests that a single measure of cancellation performance (e.g. number of omissions) can reflect multiple constructs (e.g. spatial and non-spatial deficits). This observation raises the question to what extent measures of cancellation performance reflect the spatial bias versus non-spatial errors.

Construct representation versus nomothetic span

Construct validity can be divided into *construct representation* and *nomothetic span* (Embretson, 1983). Embretson defines construct representation as identification of the cognitive processes that underlie task performance, while she defines nomothetic span as the network of correlations of one measure with other measures. In psychology, nomothetic span is often the only aspect of construct validity that is assessed.

However, convergence / divergence among different measures merely indicates that the different measures reflect (or do not reflect in the case of divergent validity) a similar construct. In contrast to construct representation, nomothetic span does not inform us about the true construct underlying behavior (Embretson, 1983). Embretson (1983) suggests that construct representation must be investigated by comparing the predictive strength of different cognitive models of test performance. Here, we do not aim to investigate which cognitive constructs explain cancellation performance. Rather, we want to investigate which behavioral construct(s) (e.g. spatial bias versus non-spatial errors) are represented by cancellation performance measures. As cancellation performance measures are often assumed to represent the spatial bias in cancellation performance, it is important to assess to what extent this construct is represented by the cancellation performance measures.

Monte Carlo simulations as a tool to study construct representation

To investigate the construct representation of a measure, one needs to know the ground truth of the underlying construct. We propose that Monte Carlo simulations are an interesting tool to study the construct representation of cancellation performance measures, as this method allows full control and knowledge over the constructs that underlie test performance. Monte Carlo simulation is a tool to carry out an elaborate inferential process by using random numbers that follow a certain probability distribution to carry out a calculation (Beisbart & Norton, 2012). To use Monte Carlo simulations to study construct representation, one must first define a model that can predict behavioural performance. A good model should be parsimonious, able to predict behaviour (in our case, unidimensional visuospatial neglect of task-relevant stimuli) and should have conceptually meaningful parameters. The model can be used to generate fictional patterns of behaviour (e.g. responses on a cancellation task). One can generate different behavioural patterns (e.g. omitted targets in a specific area of space versus omitted targets across the entire cancellation task) by independently varying the model parameters. If the model parameters are conceptually meaningful, this approach allows to study the relation between behavioural outcomes and conceptually meaningful constructs. For instance, one can generate cancellation data from a model that represents patients with versus without spatial bias. Then, one can calculate different cancellation performance measures and see whether these measures represent the spatial bias of the model that underlies the cancellation performance. Noteworthy, given this purely theoretical approach, the validity of our inferences depends on the validity of our premises.

Aim of the study

Even though the construct validity of cancellation performance measures has been investigated by means of their convergence / divergence with other measures, we do not know the constructs represented by each of these measures. The numerous methods to quantify the spatial bias of the responses on a cancellation task (see Table 1 for some examples), highlight conflicting intuitions on how to quantify the spatial bias of cancellation responses. This lack of a standard method signals a need for more conceptual clarity about the feature(s) of the response pattern that are represented by cancellation performance measures. We will focus on cancellation performance measures that aim to represent the spatial bias instead of strategy measures, as these measures (Table 1) remain the dominant method for quantifying spatial neglect. By only focusing on cancellation tasks, we do not suggest that researchers and clinicians base their diagnosis on a single task, but rather we want to obtain a clear image of what our current cancellation performance measures can and cannot reveal about spatial biases in cancellation responses. A clear understanding of the construct representation of our current methods can help research and clinical practice further in obtaining even better diagnostic accuracy of spatial neglect and could, for instance, contribute to the interpretation of lesion-symptom mapping studies (Molenberghs, Sale, & Mattingley, 2012).

Our simulation-based approach allows us to answer the question whether a cancellation performance measure that is assumed to represent spatial bias, indeed represents spatial bias or may also represent non-spatial errors. Our simulation-based approach cannot clarify to what extent between-patient variance in cancellation performance depends on inter-individual variability in spatial or non-spatial deficits, nor can this approach clarify which cognitive processes are involved in cancellation performance. Nevertheless, we must first know to what extent measures of cancellation performance reflect spatial or non-spatial deficits, before studying how spatial and non-spatial processes contribute to between-patient variance in cancellation performance.

Method

Modelling cancellation response patterns

In the next section, we aim to provide more conceptual clarity, by discussing which features of cancellation performance could be represented by cancellation performance measures.

Features of response patterns

We hypothesize that missed targets (omissions) on a cancellation task can be due to a spatial or a non-spatial deficit. The patient can omit targets in one specific area of the cancellation display (spatial errors) or can omit targets spread over the entire cancellation display (non-spatial errors). This difference is illustrated in Figure 1, where we visualize four patterns of fictional responses on a cancellation task (only including the targets).

The omissions made by Patient 1 (more spatial errors) are more densely located in the left field as compared to the omissions made by Patient 4 (more non-spatial errors). Additionally, one can see that there is a larger difference in the number of cancelled targets for the left and right side of the cancellation task for Patients 1 and 3 as compared to Patient 2 and 4. Furthermore, the cancelled targets are clustered in a smaller region of space for Patient 3 compared to Patient 1. This visualization should clarify that we can disentangle three conceptually meaningful features of the response pattern: (1) the magnitude of the difference in the number of cancelled targets of one area of space compared to another area (*spatial asymmetry*), (2) the size of the area in the cancellation display where target detection is reduced (*neglected region size*) and (3) the total number of omissions that are spread across the cancellation task (*non-spatial errors*). Patients may vary in these features, in which those patients with a strong spatial asymmetry and a large neglected region have the most severe spatial attention deficit (e.g., Patient 3 in Figure 1).

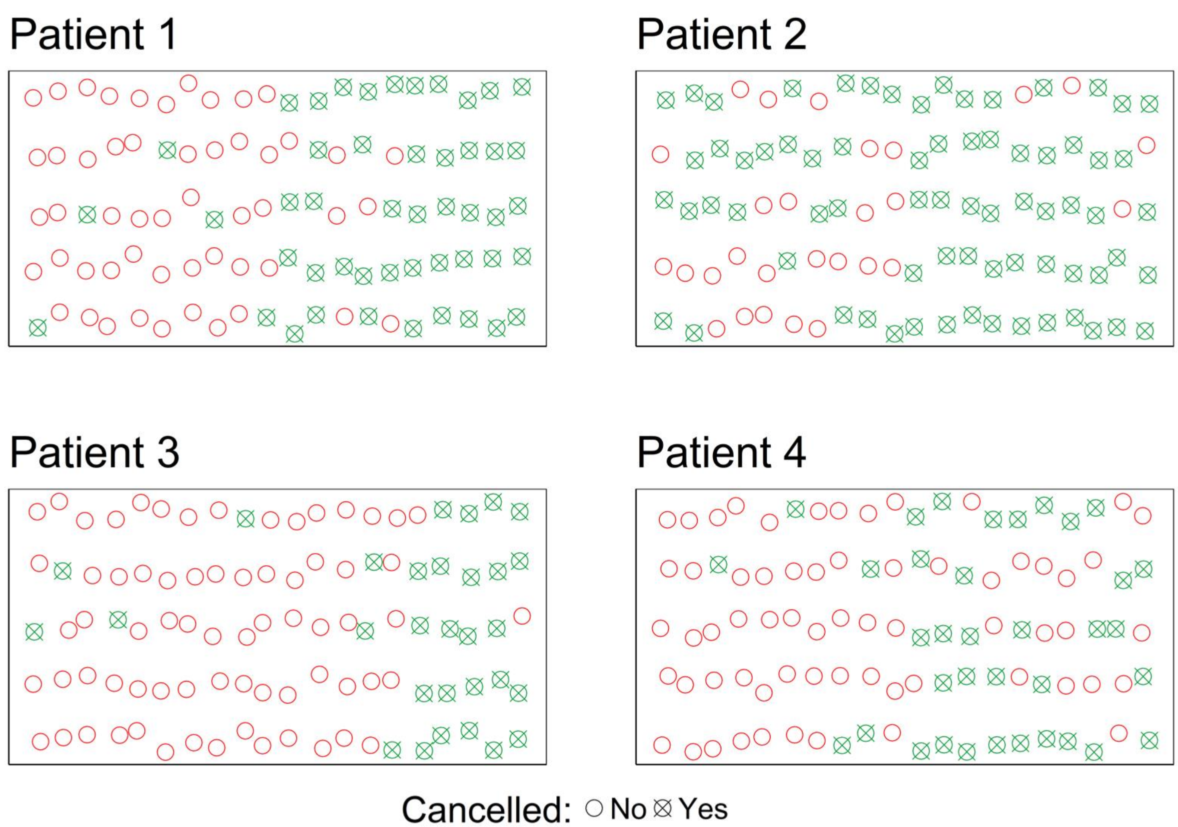

Figure 1. Examples of responses on a cancellation task with 100 targets for 4 hypothetical patients with left-sided neglect. The red open circles indicate the omissions (missed targets) and the green crossed circles represent the hits (cancelled targets).

A model of target cancellation response patterns

To reflect these conceptually meaningful features of target cancellation response patterns, we propose a simple model of cancellation data. Our model assumes that for each individual target in the search array, there is a specific probability (denoted by the symbol θ) that the patient cancels the target. This probability can take any value between 0 and 1. Responses to each target are thus assumed not to be deterministic (i.e., a target cancelled on a first test administration will not necessarily be cancelled upon retesting), but the result of a probabilistic process (akin to a coin toss). The latter implies variability in cancellation performance across test administrations. Cancellation performance is modelled by two probabilities $\theta_{Neglected\ Region}$ and $\theta_{Good\ Region}$. The $\theta_{Neglected\ Region}$ represents the probability that a target located in the neglected region is cancelled, which covers a specific domain of horizontal coordinates. The $\theta_{Good\ Region}$ reflects the probability that a target located outside of the neglected region is cancelled, which also covers a specific domain of horizontal coordinates. For patients without spatial neglect (no spatial asymmetry) the values of $\theta_{Neglected\ Region}$ and $\theta_{Good\ Region}$ are equal. For patients with spatial neglect (a spatial asymmetry) the values of $\theta_{Neglected\ Region}$ and $\theta_{Good\ Region}$ are different. Thus, spatial asymmetry is defined as the difference between $\theta_{Neglected\ Region}$ and $\theta_{Good\ Region}$. The neglected region can take any value between 0 and 1, where 0 represents a situation in which none of the targets of the cancellation task are located in the neglected region (performance across the entire domain of horizontal coordinates depends on $\theta_{Good\ Region}$) and 1 represents a situation in which all targets of the cancellation task are located in the neglected region (performance across the entire domain of horizontal coordinates depends on $\theta_{Neglected\ Region}$). If the neglected region equals 0.50, performance on half of the domain of horizontal coordinates depends on $\theta_{Good\ Region}$ and the other half depends on $\theta_{Neglected\ Region}$.

Figure 2 illustrates four different situations that can be captured by our model. The X-axis depicts the horizontal axis along the search array (-1 being the left border, 0 the centre, and 1 the right border). On the Y-axis, the response probability θ is depicted. In the case of left-sided neglect, the left side of the graph depicts $\theta_{Neglected\ Region}$, which is assumed to be constant across a certain part of space (neglected region). The right part of the graph indicates the performance level associated with $\theta_{Good\ Region}$. Spatial asymmetry refers to the performance difference between these two probabilities. In Figure 2A, for instance, the spatial asymmetry is larger compared to Figure 2B, but the same as in Figure 2C. The second parameter, the size of the neglected region, is the domain along the X-axis where $\theta_{Neglected\ Region}$ determines performance. For instance, Figure 2A represents a patient who ignores half of the page, while Figure 2C represents a patient who ignores 3/4 of the page.

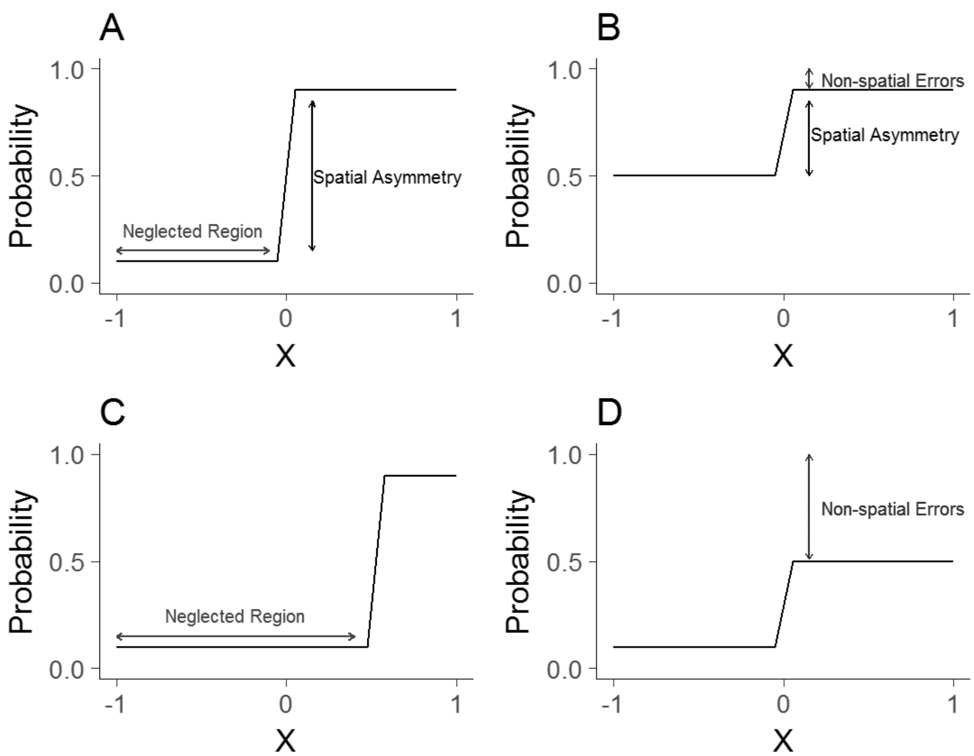

Figure 2. Examples of the model. The probability refers to the chance to cancel a target and X represents the location of the target on the horizontal axis (0 represents the center of the search array). Patient A and C have a $\theta_{\text{Neglected Region}} = .05$, $\theta_{\text{Good Region}} = .95$, Patient B has a $\theta_{\text{Neglected Region}} = .50$, $\theta_{\text{Good Region}} = .95$ and Patient D has a $\theta_{\text{Neglected Region}} = .05$, $\theta_{\text{Good Region}}$ = 0.50.

An important characteristic of our model is that $\theta_{Good\ Region}$ is not assumed to be fixed to 1, allowing for the presence of non-spatial errors (i.e., participants can also miss targets located in their good region). For instance, Figure 2B and Figure 2D only differ in the probability of making non-spatial errors (1-$\theta_{Good\ Region}$), but not in the size of the neglected region neither in the spatial asymmetry. Note that the presence of non-spatial errors not only influences performance in the good region, but extends into the neglected region.

Defining an ideal measure of cancellation performance

We argue that measuring the spatial and non-spatial components separately is important to accurately detect the presence of spatial neglect. Thus, ideally, a measure of cancellation performance isolates the spatial (*spatial asymmetry index*) from the non-spatial component (*non-spatial index*). We suggest that an ideal spatial asymmetry index should represent the interaction of the spatial asymmetry and neglected region size and should not represent the non-spatial errors, while a non-spatial index of cancellation performance should only represent the non-spatial errors and should not represent the spatial components. The latter does not imply that the spatial and non-spatial errors cannot covary in empirical data, but rather that a measure that is assumed to represent the spatial asymmetry should only represent the spatial asymmetry and should not also represent non-spatial errors.

In Figure 3A and Figure 3C the properties of this ideal spatial asymmetry index are visualized. The ideal spatial asymmetry index is represented by the colours in the two heatmaps. In Figure 3A, the spatial asymmetry (depicted on the x-axis) and neglected region size (depicted on the y-axis) vary, while the non-spatial errors are set to a constant value of 0 (corresponding to no non-spatial errors). In Figure 3C, the spatial asymmetry (depicted on the x-axis) and non-spatial errors (depicted on the y-axis) vary, while the neglected region size is set to a constant value of 0.5 (corresponding to neglecting half of the cancellation page). The contour plot in Figure 3C has a triangular shape, because a high probability of omitting targets across the entire cancellation page excludes the possibility of having a large difference in performance for two areas of space (the sum of the spatial asymmetry and non-spatial errors cannot exceed 1). Each location in these two-dimensional heatmaps corresponds to a specific model underlying cancellation performance of which four examples are depicted in Figures 3B and 3D.

We propose that the spatial asymmetry index should increase when either the spatial asymmetry or the size of the neglected region increases, and that it should reach maximal values when both are high (indicating severe spatial neglect) (Figure 3A). In contrast, the spatial asymmetry index should not change as a function of non-spatial errors (Figure 3C), i.e. for each asymmetry value, there is a unique spatial asymmetry index that does not covary with the non-spatial errors.

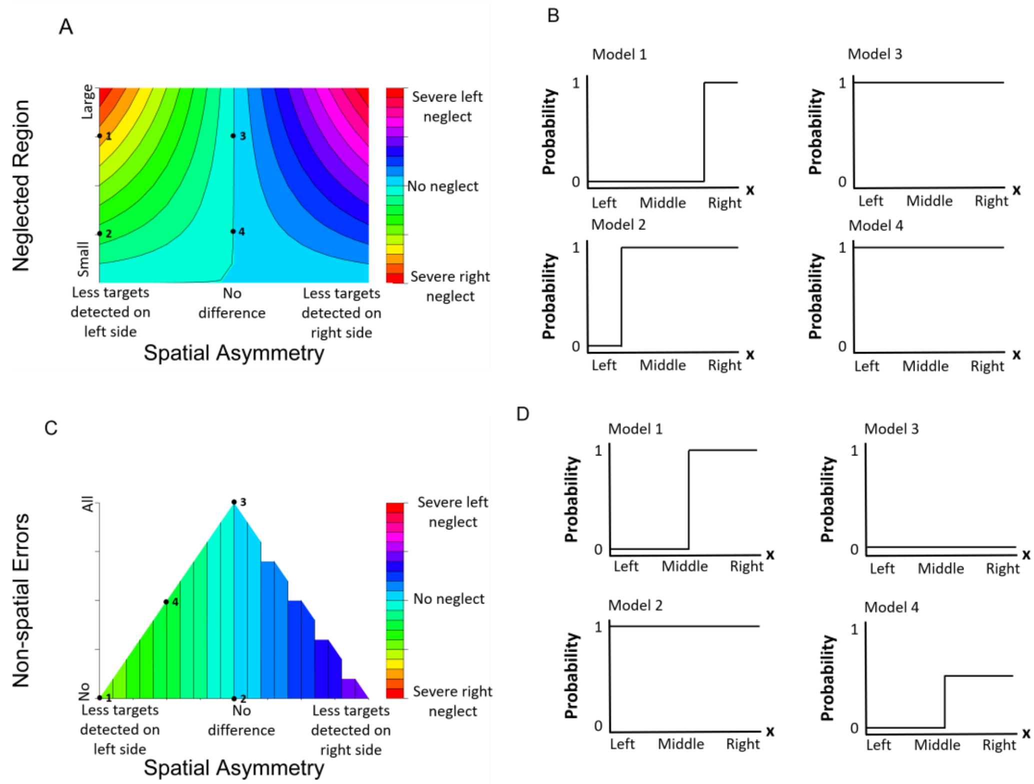

Figure 3. Panel A represents the ideal spatial asymmetry index (colors) as a function of the spatial asymmetry and neglected region size for a constant level of non-spatial errors equal to zero. The spatial asymmetry is the difference between the $\theta_{Neglected\ Region}$ and $\theta_{Good\ Region}$. The neglected region size represents the domain of target locations for which performance depends on $\theta_{Neglected\ Region}$. The four dots in panel A locate the four models shown in panel B. Models 1 and 2 differ in their neglected region size and have a maximal spatial asymmetry. Models 3 and 4 are examples of no spatial asymmetry. In panel A one can see that a larger spatial asymmetry and a larger neglected region are associated with a more extreme value (red colours) of the ideal spatial asymmetry index. The heighest values of the spatial asymmetry index (red colours) are located in the parts of the heatmap that correspond to large spatial asymmetries and large neglected regions. The lowest values of the spatial asymmetry index (blue colours) are located in the centre of the heatmap where the spatial asymmetry is lowest. Panel C represents the ideal spatial asymmetry index as a function of the non-spatial errors and spatial asymmetry for a neglect region size in which the patient would ignore half of the page. The heatmap in panel C has a triangular shape as the sum of the spatial asymmetry and non-spatial errors cannot exceed 1. The four dots in panel C locate the four models shown in panel D. Models 1 and 2 differ in their spatial asymmetry, but not in their non-spatial errors. Models 2 and 3 only differ in their non-spatial errors, while models 1 and 4 differ both in spatial asymmetry and non-spatial errors. Panel C shows how the ideal spatial asymmetry index becomes more extreme (red colours) as the spatial asymmetry increases, and that the spatial asymmetry index has a constant value when the non-spatial errors vary.

Simulations

Step 1. Generating cancellation data

A uniform distribution ranging from -1 to +1 was used to generate 50 target locations (**Error! Reference source not found.**A). Cancelled distractors (false alarms) are typically not taken into account when summarizing cancellation data to detect egocentric spatial neglect. Therefore, responses to distractors were not simulated. For each target location, a cancelled target (hit) or a omitted target (miss) was drawn at random from a Bernoulli distribution (Figure 4B). The probability of the Bernoulli distribution was determined by our simple model of cancellation performance. This model is characterized by three parameters: $\theta_{Neglected\ Region}$, $\theta_{Good\ Region}$ and the location of the boundary between the neglected and good region (denoted by the symbol δ) (Figure 4B). If the target location was smaller or equal to the location of the boundary between the neglected and good region (δ), the hits or misses were drawn from a Bernoulli distribution with $\theta_{Neglected\ Region}$ as the probability of a hit. If the target location was larger than the location of the boundary (δ), the hits or misses were drawn from a Bernoulli distribution with $\theta_{Good\ Region}$ as the probability of a hit (Figure 4B).

The spatial asymmetry, neglected region size and non-spatial errors can be inferred from the three model parameters. The spatial asymmetry is the difference between the $\theta_{Neglected\ Region}$ and $\theta_{Good\ Region}$. If the neglected region was located on the left side, the spatial asymmetry value was multiplied by -1. This resulted in a spatial asymmetry index ranging from -1 (left-sided neglect) to 1 (right-sided neglect), with 0 indicating no neglect. The neglected region size was calculated on the basis of δ and ranges from 0 (0% of the page is ignored, thus all target locations are located in the good field) to 1 (100% of the targets are in the neglected region). The non-spatial errors were calculated by taking the difference between the maximum probability of 1 and the $\theta_{Good\ Region}$.

We generated cancellation data for each combination of unique values of $\theta_{Neglected\ Region}$, $\theta_{Good\ Region}$ and δ. $\theta_{Neglected\ Region}$, $\theta_{Good\ Region}$ each ranged from 0 to 1 in 10 steps. The location of the boundary between the neglected and good region (denoted by the symbol δ) ranged from -1 to 1 in 10 steps (Figure 4B). Then, for each unique combination of model parameters ($\theta_{Neglected\ Region}$, $\theta_{Good\ Region}$ and δ), different cancellation performance measures were calculated (Figure 4C). This procedure was repeated 10,000 times. Across these 10,000 iterations the average value of each cancellation performance measure was calculated to obtain the expected value.

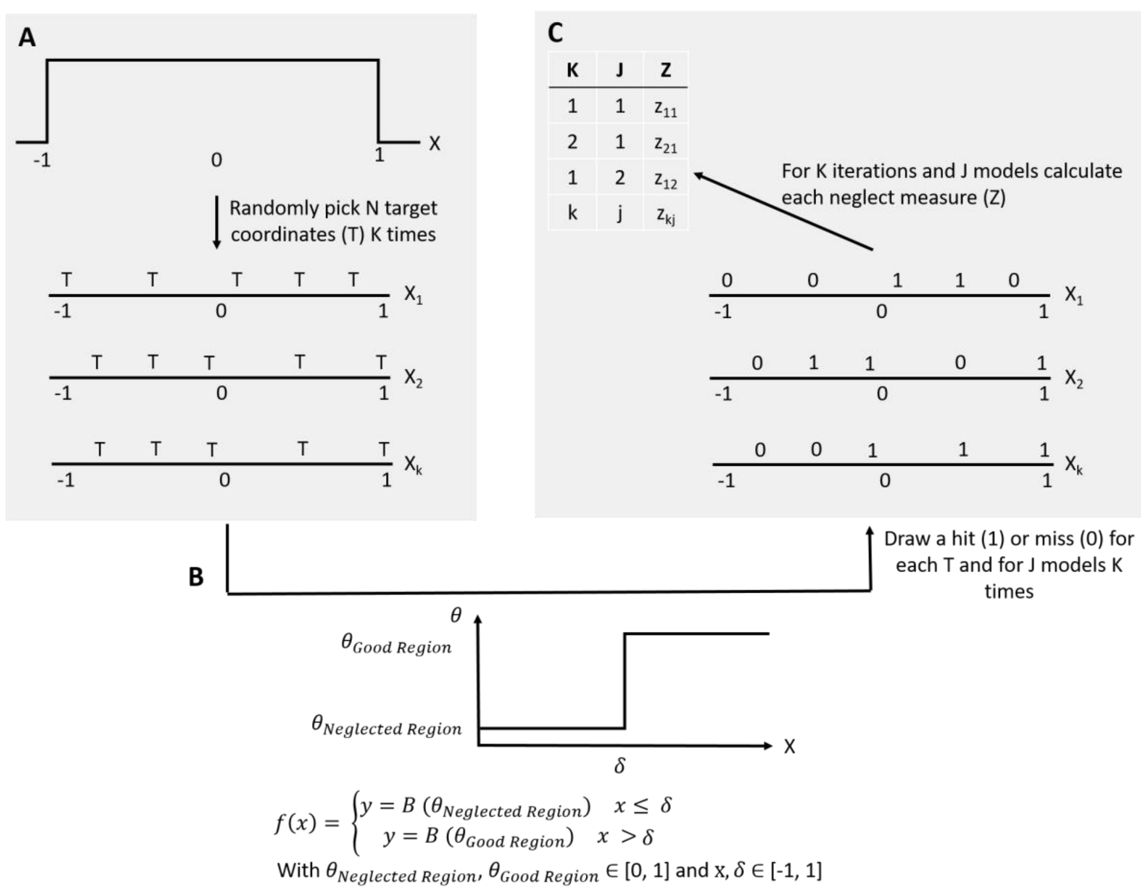

Figure 4. Schematic representation of the procedure of the simulations. In the first step (panel A) a number (N) of random target coordinates (T) were drawn from a uniform distribution. This procedure was repeated a specific number (K) of times. In the second step (panel B) a hit or miss was generated according to our model (represented in the equation) for each target location and each unique combination of model parameters. Based on these hits and misses the CP measures were calculated (panel C).

Step 2. Calculating measures of spatial neglect

We selected cancellation performance measures that are often used to summarize responses on cancellation tasks to diagnose spatial neglect (also listed in Table 1): (1) the total number of omissions (*O;* Albert, 1973), (2) the number of contralesional omissions (*Con O;* Bailey et al., 2004; Gauthier et al., 1989; Weintraub, 1985), (3) the number of contralesional cancellations divided by the total number of cancellations (*Con H / H;* Friedman, 1992), (4) the difference between left and right cancellations (*L-R;* Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015), (5) the difference between left and right cancellations divided by the total number of cancellations (*L-R / H;* McIntosh, Brodie, Beschin, & Robertson, 2000), (6) the left cancellations divided by the right cancellations (*L/R;* Dalmaijer et al., 2014) and (7) the centre of cancellation, which is the average horizontal coordinate of all cancelled targets minus the average horizontal coordinate of all targets (*CoC*; Rorden & Karnath, 2010; Vaes et al., 2015). Some of these measures were linearly transformed to make the ranges of the different measures independent of the number of targets of the cancellation task: (1) the number of omissions were divided by the total number of targets and therefore values range from 0, which indicates no omissions, to 1, which indicates that all targets were omitted, (2) the number of contralateral omissions were divided by half of the total number of targets, which makes the values range from 0, indicating no contralateral omissions, to 1, indicating that all contralateral targets were omitted, (3) the left minus right difference was divided by half of the total number of targets, which makes the values range from -1, indicating that there were no hits on the left side and that all targets were cancelled on the right side, to 1, indicating that all targets were cancelled on the left side and that there were no hits on the right side.

Step 3. Evaluating the construct representation

To evaluate the construct representation of the cancellation performance measures, we visualized their value (indicated by colours) as a function of the spatial asymmetry (depicted on the x-axis) and the neglected region size (depicted on the y-axis) for the case with no non-spatial errors (identical to the visualization in Figure 3A). Additionally, we visualized the value of all cancellation performance measures as a function of the spatial asymmetry (depicted on the x-axis) and the non-spatial errors (depicted on the y-axis) for a neglected region size of 0.5 (identical to the visualization in Figure 3C). We then compared the properties of each cancellation performance measure to the properties of the ideal spatial asymmetry index that we defined earlier (Figure 3A and 3C). For ease of comparison we added a duplicate of Figure 3A and 3C in the results figure (Figure 5A). The colour scales were designed in a way that the red end of the colour spectrum always represent values of the cancellation performance measure that would indicate severe spatial neglect and that cyan and light green colours indicate values of the cancellation performance measure that would not indicate spatial neglect.

Step 4. Evaluating the goodness of fit

In addition, we evaluated the goodness of fit of each cancellation performance measure in comparison to the ideal spatial asymmetry index. We estimated the R-squared on the basis of several separate linear regressions where the ideal spatial asymmetry index was predicted by one of the cancellation performance measures. For cancellation performance measures that do not have a different value for left versus right-sided neglect, we predicted the absolute value of the ideal spatial asymmetry index. For the L/R score, we logarithmically transformed the L/R score to estimate the R-squared. Note that the evaluation of the goodness of fit was done on the expected values of the cancellation performance measures, therefore the R-squared is not affected by sampling error. Thus, in this case, the goodness of fit was only affected by bias in the measures.

Results and discussion

Construct representation

The results are visualized in Figure 5. For each cancellation performance measure, two contour plots are presented next to each other. The contour plots on the left side of each panel represent the relation between the cancellation performance measure (represented by the colours) and the spatial asymmetry (x-axis) and neglected region size (y-axis). For these contour plots the non-spatial errors are equal to 0. The contour plots on the right side of each panel represent the relation of the cancellation performance measure (represented by the colours) to the spatial asymmetry (x-axis- and non-spatial errors (y-axis). For these contour plots, the neglected region size has a constant value of 0.5. Figure 5A represents the expected relation of the ideal spatial asymmetry index to the spatial asymmetry, neglected region size and non-spatial errors. Figure 5B to 5H represent the expected relation of different cancellation performance measures to the spatial asymmetry, neglected region size and non-spatial errors.

Figure 5 clarifies how all cancellation performance measures have different properties than those outlined for the ideal spatial asymmetry index that we defined earlier (Figure 5A depicts the ideal measure). For the interaction between the non-spatial errors and spatial asymmetry, the measures O (**Error! Reference source not found.**B), Con O (**Error! Reference source not found.**C) and Con H / H (**Error! Reference source not found.**D) reached a maximum value when there was absolutely no spatial asymmetry, but a high non-spatial error margin (red colors on the tip of the pyramidal contour plots). Thus O, Con O and Con H / H had the same value for cases who have a severe spatial attention deficit and for cases who have a severe non-spatial attention deficit. Thus, cancellation performance measures that do not explicitly compare the contra- and ipsilesional side of the search array or that do not take into account the location of the hits or omissions were unable to dissociate between a high non-spatial error margin and a strong spatially biased response pattern.

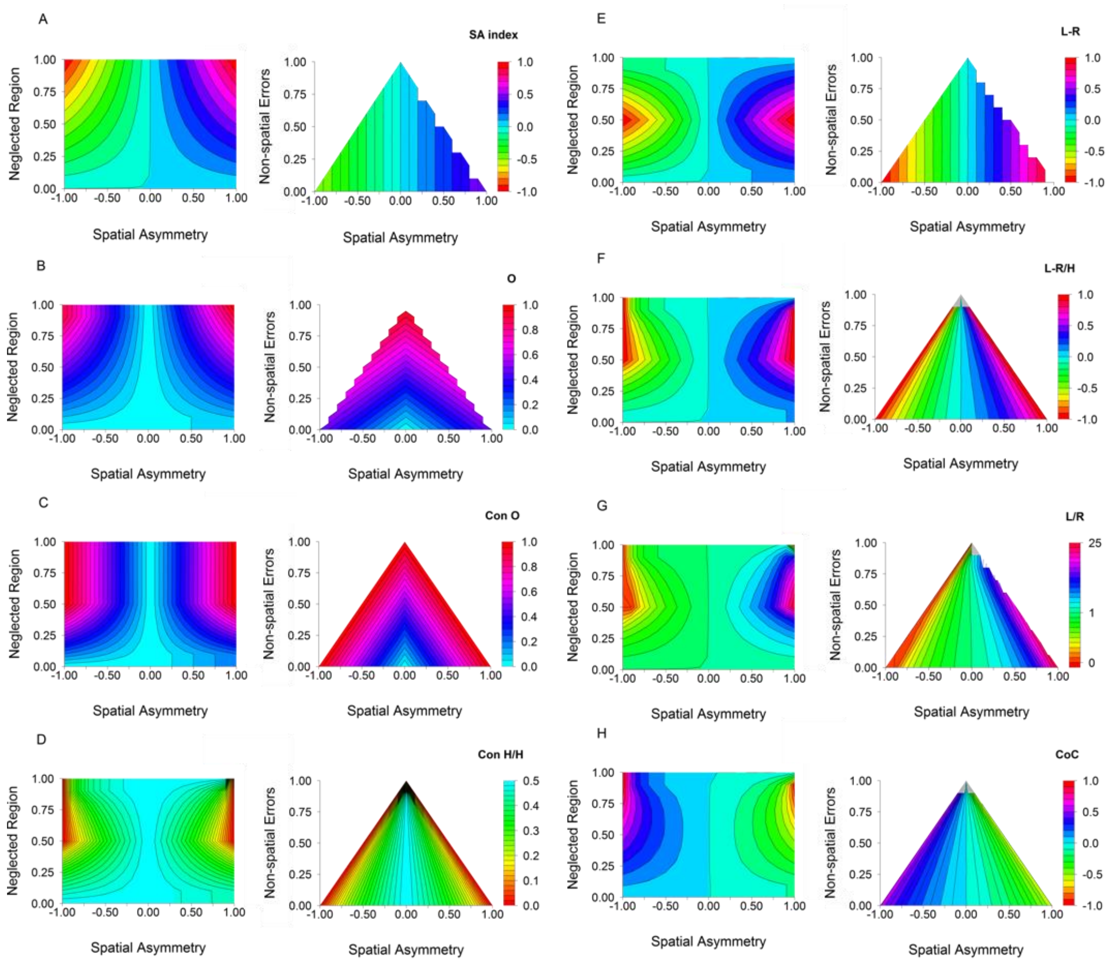

Figure 5. Contour plots of the different CP measures (represented by the colors) as a function of the spatial asymmetry and neglected region size (columns 1 and 3) and as a function of the spatial asymmetry and non-spatial errors (columns 2 and 4). The neglected region size can vary from 0 (0% of the page is ignored) to 1 (100% of the page is ignored). The spatial asymmetry can range from -1 (left sided neglect) to +1 (right sided neglect) and 0 indicating no neglect. The non-spatial errors can vary from 0 (no non-spatial errors, perfect performance in the good field) to 1 (maximum number of non-spatial errors, no targets detected in good field).). For the figures in columns 1 and 3, the spatial asymmetry and neglected region size vary, while the non-spatial errors were kept at a constant value of 0. For the figures in columns 2 and 4, the spatial asymmetry and non-spatial errors vary, while the neglected region size was kept constant at a value of 0.5 (half of the page is neglected). Each panel displays two contour plots for each CP measure. The first two plots (panel A) represent the ideal spatial asymmetry index derived by multiplication of the spatial asymmetry and neglected region size (a duplicate of **Error! Reference source not found.**A and 3C). Panels B to H each represent the relation of a CP measure (indicated by the colors) to the three model parameters. The color scales are designed in such way that green and cyan colors represent values of the measure that would not indicate neglect, while red colors represent values of the measure that would indicate severe neglect. O = total proportion of omissions, Con O = total proportion of contralateral omissions, Con H / H = contralateral hits divided by total hits, L-R = difference in proportion of hits between left and right side, L-R / H = difference in proportion of hits between left and right side divided by

total proportion of hits, L/R = ratio between proportion of hits on left versus right side and CoC = standardized average location of cancelled targets.

Consequently, in order to differentiate between the spatial and non-spatial sources of omissions, an explicit comparison between the contra- and ipsilesional side of the search array must be made or the location of the errors must be taken into account. However, the results show that representing the spatial pattern of omissions is not straightforward. Figure 5 illustrates that measures that explicitly compare the left and right side of the cancellation pattern (L-R, L-R/H, L/R) depend on the spatial asymmetry (the contours are not perpendicular to the x-axis). The L-R, L-R/H and L/R values were indeed larger when the spatial asymmetry was larger (**Error! Reference source not found.**E, **Error! Reference source not found.**F and **Error! Reference source not found.**G). However, these measures did not accurately reflect the ideal spatial asymmetry index when the neglected region extended into the ipsilesional field. That is, the values for L-R, L-R/H and L/R were highest when the spatial asymmetry was largest and the neglected region affected half of the page, whereas the values became smaller when the neglected region extended further into the ipsilesional field (in **Error! Reference source not found.**E, **Error! Reference source not found.**F and **Error! Reference source not found.**G the red colors are not located in the upper left and upper right corners of the rectangular contour plot). In addition, although the L-R/H and L/R measures compare performance between the two test halves, the values of these measures also depended on the non-spatial errors (in **Error! Reference source not found.**F and **Error! Reference source not found.**G the contours are not perpendicular to the y-axis in the pyramidal contour plot) in contrast to L-R (in **Error! Reference source not found.**E the contours are perpendicular to the y-axis in the pyramidal contour plot). These results suggest that dividing the score by the total cancelled targets or the cancelled targets on half of the test introduced a dependency on the non-spatial errors.

Since the CoC does not rely on a comparison of two halves of the test page, but takes into account the location of all cancelled targets, it was suggested that it would be better at measuring neglect when it affects more than half of the page (Rorden & Karnath, 2010). The results of our simulation indeed show that the CoC reached a more extreme value if the neglected region extended into the ipsilesional field compared to a smaller neglected region (in **Error! Reference source not found.**H the red colors are mostly located in the upper left and right corners of the rectangular contour plot). However, this pattern was not consistent across the entire range of spatial asymmetries. Furthermore, the CoC also seemed to be dependent on the non-spatial errors. Thus, in some cases higher values of the CoC can represent more non-spatial errors rather than more spatial errors.

Goodness of fit

The results on the goodness of fit are visualized in Figure 6 and presented in Table 2. The R-squared ranged from a minimum of 14% to a maximum of 62% explained variance. The worst fitting indices were the cancellation performance measures that do not make an explicit comparison between performance on the left and right side of the visual field (O, Con O and Con H / H). All these cancellation performance measures had an R-squared lower than 30%, while the other cancellation performance measures had an R-squared higher than 50%, except for the L/R score which only had an R-squared of 18%. The L-R score corrected for the total hits produced a slight gain of 7% explained variance compared to the raw L-R score. The CoC fitted best with our ideal spatial asymmetry index (R-squared = 62%).

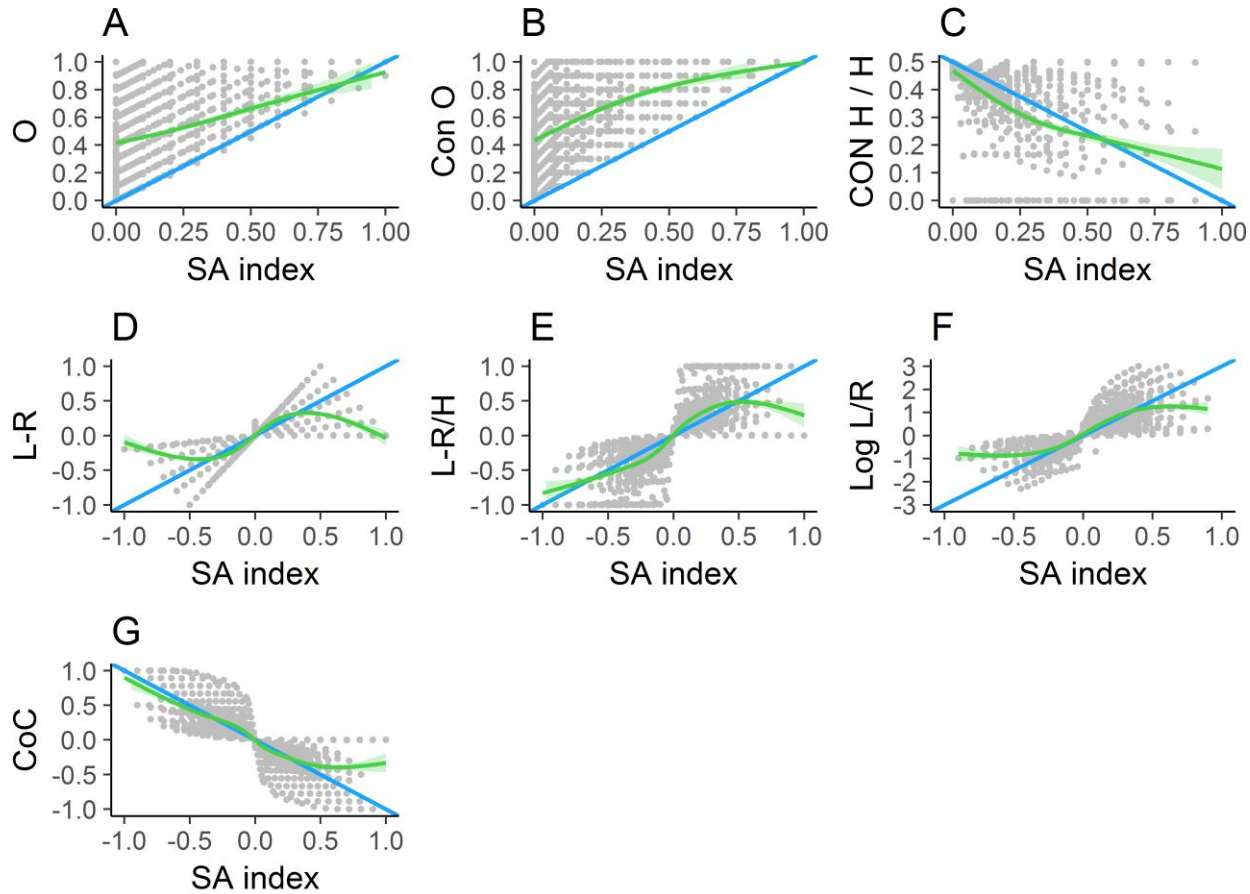

Figure 6. The scatterplots of each CP measure with the ideal spatial asymmetry index (SA index). In each plot the blue line represents a perfect fit between the CP measure and the ideal spatial asymmetry index. The green line represents the generalized linear model fit and the green area represents the standard error of the generalized additive model. O = total proportion of omissions, Con O = total proportion of contralateral omissions, Con H / H = contralateral hits divided by total hits, L-R = difference in proportion of hits between left and right side, L-R / H = difference in proportion of hits between left and right side divided by total proportion of hits, L/R = ratio between proportion of hits on left versus right side and CoC = standardized average location of cancelled targets.

Table 2. Linear regression results for measuring goodness of fit of cancellation summary measures.

Predictor	Outcome	Intercept	Slope			R-squared (%)
			Estimate	T	P	
O	Absolute SA Index	0.04	0.28	14.97	< .001	14
Con O		-0.03	0.35	21.60		26
Con H / H		0.44	-0.70	-24.13		30
L-R	SA Index	0.00	0.76	37.21		51
L-R / H		0.00	0.54	43.10		58
Log L / R		0.02	0.05	17.04		18
CoC		0.00	-0.73	-47.00		62

Table Note. O = total proportion of omissions, Con O = total proportion of contralateral omissions, Con H / H = contralateral hits divided by total hits, L-R = difference in proportion of hits between left and right side, L-R / H = difference in proportion of hits between left and right side divided by total proportion of hits, L/R = ratio between proportion of hits on left versus right side and CoC = standardized average location of cancelled targets. SA Index = ideal spatial asymmetry index derived from multiplying spatial asymmetry and neglected region size from the model underlying the cancellation data. T = t-value and P = p-value.

General Discussion

Different methods have been used to measure the spatial bias in cancellation performance. However, until now, it was unclear to what extent different measures represent different features of cancellation performance. For these reasons we developed a simple model and proposed conceptually meaningful features — non-spatial errors, spatial asymmetry and the neglected region size— of cancellation performance and we explored the relation of commonly used measures of cancellation performance to these features. This simulation study demonstrated that the different cancellation performance measures that are often used to diagnose spatial neglect represented different features of the cancellation response pattern. This illustrates conceptually meaningful heterogeneity in how spatial neglect is quantified. Second, our study revealed that none of the different cancellation performance measures had a simple relation to the interaction between the spatial asymmetry and neglected region size, which we defined as the ideal spatial asymmetry index. Our analysis on the goodness of fit of the different cancellation performance measures revealed that the cancellation performance measures that do not explicitly compare the performance between the left and right side had the weakest fit and that the CoC (Rorden & Karnath, 2010) had the best fit. Taken together, the results revealed that the L-R score was the only measure that was completely independent of the non-spatial errors and that, although the CoC also reflected non-spatial errors to some extent, the CoC had the best fit with respect to the ideal spatial asymmetry index since it can account for differences in neglected region sizes.

Implications

Our study revealed that numerous cancellation performance measures are dependent on non-spatial errors. The latter result has particular importance for studies that aim to isolate the spatial from the non-spatial attention deficits. For instance, van Kessel and colleagues investigated the relation between visuospatial asymmetries and non-spatial attention in subacute stroke patients (van Kessel, van Nes, Brouwer, Geurts, & Fasotti, 2010). The authors found no improvement in diagnostic sensitivity of spatial neglect based on an asymmetry score calculated on the basis of the Behavioral Inattention Test (BIT) star cancellation task compared to a raw omission score for the right hemisphere stroke group. However, the asymmetry score that was calculated on the basis of the BIT compared the performance between the left and right field and corrected this difference by the total number of cancellations (L-R / H). Based on our simulation we can expect that this asymmetry score and the raw omission score (O) are both affected by non-spatial error sources on cancellation tasks and consequently we would not necessarily expect better diagnostic sensitivity for spatial neglect based on L-R/H compared to O. We chose this study to illustrate the implications of our theoretical validation, but the implications can be expected to affect other studies that aim to dissociate spatial from non-spatial attention deficits in spatial neglect.

Limitations

For the current study, we used a simple step function to model unidimensional visuospatial neglect of task-relevant stimuli (cancelled targets). Some may argue that the choice for this model is unrealistic. Indeed, it has been suggested that spatial neglect is characterized by a spatial attention gradient (e.g. Chatterjee et al., 1999; Smania et al., 1998), in which performance gradually worsens for targets located more in the periphery of the contralesional field. As our step model cannot represent the possibility that patients may vary in the extent to which they exhibit a gradual or sudden change in performance on the cancellation task, we performed additional simulations on the basis of a model that allowed to represent these possible between-patient differences. The results of these supplementary simulations on the basis of a gradient model are highly similar to the results based on the step model (Supplementary 1).

In this study, we focused on asymmetries in the horizontal dimension. However, there may also be cases in which performance depends both on the horizontal and vertical target location. In these cases the neglected region may be restricted to a certain quadrant of the cancellation page (Mark & Monson, 1997). The current study did not aim to clarify the relationship between typical measures of cancellation performance and the occurrence of neglect for a quadrant of space. Noteworthy, the cancellation performance measures that are typically used in clinical practice focus on unidimensional spatial neglect. Our study revealed that the measures used to quantify the horizontal spatial attention deficits did not have the properties of an ideal measure of a unidimensional spatial attention deficit. Future studies should explore how to best quantify multidimensional spatial biases.

In addition, we did not simulate responses to distractors, as typical measures of cancellation performance do not take into account this additional source of information. Distractors can affect performance (e.g.

Molenberghs, Gillebert, Peeters, & Vandenberghe, 2008; Gillebert et al., 2011) and be informative about the cognitive deficits experienced by the patient. According to the current measures of cancellation performance, no distinction is made between a patient who cancels 10 targets and 5 distractors and a patient who cancels 10 targets and 0 distractors on the left side of the page. However, one may argue that performance of the first patient is worse than performance of the second patient. Several factors can contribute to the cancellation of distractors (e.g. object-based selective attention deficits or lower level visual problems). In the future, it should be explored how to quantify and interpret information about cancelled distractors when assessing spatial neglect.

In addition, we designed a model that treats the neglected region, non-spatial errors and spatial asymmetry as independent factors. That is, our model makes no assumptions on the associations between the three parameters and thus imposes no structure on the covariance of these parameters. In stroke patients, these parameters may co-vary. For instance, it has been suggested that sustained attention deficits aggravate the spatial attention bias (Corbetta, 2014). However, it is undesirable to impose assumptions of covariance on the model as this would not allow to estimate the parameters independently from each other. That is, only when the parameters are estimated independently from each other, the natural (and not imposed by the model) covariance of the parameters in the stroke population can be studied.

Future research

Given the fact that none of the measures of spatial neglect discussed in the current study had the features of an ideal unidimensional spatial asymmetry index (independence of non-spatial errors and accurate representation of neglected region size and spatial asymmetry), it is interesting to further investigate the possibility to estimate the spatial asymmetry, neglected region size and non-spatial errors on the basis of modelling cancellation data. To account for two-dimensional neglect, our model can be extended to a two-dimensional step function that includes the horizontal and radial dimension. Furthermore, the fit of the gradient model (described in Supplementary 1) could be compared to the fit of the step model to test whether patients vary in the gradualness of their spatial biases on cancellation tasks. Through parameter estimation more information from the cancellation response pattern can be extracted which may lead to more specific diagnosis of attention deficits. It may also result in more insight in the relation between spatial and non-spatial attention deficits and how both relate to functional outcome.

References

Albert, M. L. (1973). A simple test of visual neglect. *Neurology*, *23*(6), 658–664. https://doi.org/10.1212/WNL.23.6.658

Azouvi, P., Bartolomeo, P., Beis, J.-M., Perennou, D., Pradat-Diehl, P., & Rousseaux, M. (2006). A battery of tests for the quantitative assessment of unilateral neglect. *Restorative Neurology and Neuroscience*, *24*(4–6), 273–285.

Bailey, M. J., Riddoch, M. J., & Crome, P. (2004). Test–retest stability of three tests for unilateral visual neglect in patients with stroke: Star Cancellation, Line Bisection, and the Baking Tray Task. *Neuropsychological Rehabilitation*, *14*(4), 403–419. https://doi.org/10.1080/09602010343000282

Bartolomeo, P., Thiebaut de Schotten, M., & Chica, A. B. (2012). Brain networks of visuospatial attention and their disruption in visual neglect. *Frontiers in Human Neuroscience*, *6*. https://doi.org/10.3389/fnhum.2012.00110

Beisbart, C., & Norton, J. D. (2012). Why Monte Carlo Simulations Are Inferences and Not Experiments. *International Studies in the Philosophy of Science*, *26*(4), 403–422. https://doi.org/10.1080/02698595.2012.748497

Bisiach, E., Luzzatti, C., & Perani, D. (1979). Unilateral neglect, representational schema and consciousness. *Brain : A Journal of Neurology*, *102*(3), 609–618. https://doi.org/10.1093/brain/102.3.609

Bowen, A., McKenna, K., & Tallis, R. C. (1999). Reasons for Variability in the Reported Rate of Occurrence of Unilateral Spatial Neglect After Stroke. *Stroke*, *30*(6), 1196–1202. https://doi.org/10.1161/01.STR.30.6.1196

Cazzoli, D., Nyffeler, T., Hess, C. W., & Müri, R. M. (2011). Vertical bias in neglect: A question of time? *Neuropsychologia*, *49*(9), 2369–2374. https://doi.org/10.1016/j.neuropsychologia.2011.04.010

Chatterjee, A., Thompson, K. A., & Ricci, R. (1999). Quantitative Analysis of Cancellation Tasks in Neglect. *Cortex*, *35*(2), 253–262. https://doi.org/10.1016/S0010-9452(08)70798-6

Corbetta, M. (2014). Hemispatial Neglect: Clinic, Pathogenesis, and Treatment. *Seminars in Neurology*, *34*(05), 514–523. https://doi.org/10.1055/s-0034-1396005

Corbetta, M., & Shulman, G. L. (2011). SPATIAL NEGLECT AND ATTENTION NETWORKS. *Annual Review of Neuroscience*, *34*, 569–599. https://doi.org/10.1146/annurev-neuro-061010-113731

Dalmaijer, E. S., Stigchel, S. V. der, Nijboer, T. C. W., Cornelissen, T. H. W., & Husain, M. (2014). CancellationTools: All-in-one software for administration and analysis of cancellation tasks. *Behavior Research Methods*, *47*(4), 1065–1075. https://doi.org/10.3758/s13428-014-0522-7

Demeyere, N., Riddoch, M. J., Slavkova, E. D., Bickerton, W.-L., & Humphreys, G. W. (2015). The Oxford Cognitive Screen (OCS): Validation of a stroke-specific short cognitive screening tool. *Psychological Assessment*, *27*(3), 883–894. https://doi.org/10.1037/pas0000082

Embretson, S. (1983). Construct validity: Construct representation versus nomothetic span. *Psychological Bulletin*, *93*(1), 179–197. https://doi.org/10.1037/0033-2909.93.1.179

Friedman, P. J. (1992). The Star Cancellation Test in acute stroke. *Clinical Rehabilitation*, *6*(1), 23–30. https://doi.org/10.1177/026921559200600104

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The bells test: a quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology*.

Gillebert, C. R., Mantini, D., Thijs, V., Sunaert, S., Dupont, P., & Vandenberghe, R. (2011). Lesion evidence for the critical role of the intraparietal sulcus in spatial attention. *Brain*, awr085. https://doi.org/10.1093/brain/awr085

Halligan, P. W., Cockburn, J., & Wilson, B. A. (1991). The behavioural assessment of visual neglect. *Neuropsychological Rehabilitation*, *1*(1), 5–32. https://doi.org/10.1080/09602019108401377

Halligan, Peter W., & Marshall, J. C. (1989). Is neglect (only) lateral? a quadrant analysis of line cancellation. *Journal of Clinical and Experimental Neuropsychology*, *11*(6), 793–798. https://doi.org/10.1080/01688638908400936

Heilman, K. M., Bowers, D., Valenstein, E., & Watson, R. T. (1987). Hemispace and hemispatial neglect. In *Advances in Psychology* (Vol. 45, pp. 115–150). New York, NY, USA: Elsevier Science. Retrieved from http://dx.doi.org/10.1016/S0166-4115(08)61711-2

Husain, M., & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience*, *4*(1), 26–36. https://doi.org/10.1038/nrn1005

Karnath, H. O. (1997). Spatial orientation and the representation of space with parietal lobe lesions. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *352*(1360), 1411–1419. https://doi.org/10.1098/rstb.1997.0127

Mark, V. W., & Monson, N. (1997). Two-Dimensional Cancellation Neglect a Review and Suggested Method of Analysis. *Cortex*, *33*(3), 553–562. https://doi.org/10.1016/S0010-9452(08)70236-3

McIntosh, R. D., Brodie, E. E., Beschin, N., & Robertson, I. H. (2000). Improving the clinical diagnosis of personal neglect: a reformulated comb and razor test. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *36*(2), 289–292. https://doi.org/10.1016/S0010-9452(08)70530-6

McIntosh, R.D. (2017). *The end of the line: Antagonistic attentional weightings in unilateral neglect*. Article in Press. https://doi.org/10.1016/j.cortex.2017.07.011

McIntosh, R. D., Schindler, I., Birchall, D., & Milner, A. D. (2005). Weights and measures: A new look at bisection behaviour in neglect. *Cognitive Brain Research*, *25*(3), 833–850. https://doi.org/10.1016/j.cogbrainres.2005.09.008

Molenberghs, P., Gillebert, C.R., Peeters, R., & Vandenberghe, R. (2008). Convergence between lesion-symptom mapping and functional magnetic resonance imaging of spatially selective attention in the intact brain. *Journal of Neuroscience, 28*(13), 3359-3373. https://doi.org/10.1523/JNEUROSCI.5247-07.2008

Molenberghs, P., Sale, M. V., & Mattingley, J. B. (2012). Is there a critical lesion site for unilateral spatial neglect? A meta-analysis using activation likelihood estimation. *Frontiers in Human Neuroscience*, *6*. https://doi.org/10.3389/fnhum.2012.00078

Pisella, L., & Mattingley, J. B. (2004). The contribution of spatial remapping impairments to unilateral visual neglect. *Neuroscience & Biobehavioral Reviews*, *28*(2), 181–200. https://doi.org/10.1016/j.neubiorev.2004.03.003

Rapcsak, S. Z., Cimino, C. R., & Heilman, K. M. (1988). Altitudinal neglect. *Neurology*, *38*(2), 277–281. https://doi.org/10.1212/WNL.38.2.277

Rorden, C., & Karnath, H.-O. (2010). A simple measure of neglect severity. *Neuropsychologia*, *48*(9), 2758–2763. https://doi.org/10.1016/j.neuropsychologia.2010.04.018

Rousseaux, M., Beis, J. M., Pradat-Diehl, P., Martin, Y., Bartolomeo, P., Bernati, T., … Azouvi, P. (2001). [Presenting a battery for assessing spatial neglect. Norms and effects of age, educational level, sex, hand and laterality]. *Revue Neurologique*, *157*(11 Pt 1), 1385–1400.

Smania, N., Martini, M. C., Gambina, G., Tomelleri, G., Palamara, A., Natale, E., & Marzi, C. A. (1998). The spatial distribution of visual attention in hemineglect and extinction patients. *Brain*, *121*(9), 1759–1770. https://doi.org/10.1093/brain/121.9.1759

Sperber, C., & Karnath, H.-O. (2016). Diagnostic validity of line bisection in the acute phase of stroke. *Neuropsychologia*, *82*, 200–204. https://doi.org/10.1016/j.neuropsychologia.2016.01.026

Vaes, N., Lafosse, C., Nys, G., Schevernels, H., Dereymaeker, L., Oostra, K., … Vingerhoets, G. (2015). Capturing peripersonal spatial neglect: An electronic method to quantify visuospatial processes. *Behavior Research Methods*, *47*(1), 27–44. https://doi.org/10.3758/s13428-014-0448-0

van Kessel, M. E., van Nes, I. J. W., Brouwer, W. H., Geurts, A. C. H., & Fasotti, L. (2010). Visuospatial asymmetry and non-spatial attention in subacute stroke patients with and without neglect. *Cortex*, *46*(5), 602–612. https://doi.org/10.1016/j.cortex.2009.06.004

Vandenberghe, R., & Gillebert, C. R. (2009). Parcellation of parietal cortex: Convergence between lesion-symptom mapping and mapping of the intact functioning brain. *Behavioural Brain Research*, *199*(2), 171–182. https://doi.org/10.1016/j.bbr.2008.12.005

Wansard, M., Meulemans, T., & Geurten, M. (2016). Shedding new light on representational neglect: The importance of dissociating visual and spatial components. *Neuropsychologia*, *84*, 150–157. https://doi.org/10.1016/j.neuropsychologia.2016.02.006

Weintraub, S. (1985). Mental state assessment of young and elderly adults in behavioral neurology. *Principles of Behavioral Neurology.*, 71–123.

Supplementary 1

Introduction

In our step model of unidimensional spatial neglect for task-relevant stimuli, performance on the cancellation task depends on two probabilities of cancelling a target, one affecting performance in the good (ipsilesional) region of space and one affecting performance in the neglected (contralesional) region of space. However, in literature, it has been suggested that performance may *gradually* change as a function of space in patients with spatial neglect. This gradient of neglect has also been empirically established (Chatterjee, Thompson, & Ricci, 1999; Dvorkin, Bogey, Harvey, & Patton, 2012; Karnath, 1994; Smania et al., 1998). To illustrate that our conclusions remain valid even when data are simulated according to a gradient model, we simulated data with a gradient model and compared these results to the original results based on our step model. In the next paragraphs, we will describe our gradient model and we will illustrate that the simulation results are not qualitatively different from the simulation results based on a step model.

Methods

Step 1. A gradient model of cancellation performance

The spatial gradient can be represented by a model in which performance gradually changes as a function of the target location according to a cumulative Gaussian function. The cumulative Gaussian has a sigmoidal shape and is often used in the domain of psychophysics (Wichmann & Hill, 2001). The cumulative Gaussian function is characterized by two parameters. The first parameter, μ, corresponds to the inflection point of the cumulative Gaussian function. The second parameter, σ, represents the steepness of the slope of the cumulative Gaussian function. Thus, a small σ corresponds to a sudden change in performance as a function of the target location, while a large σ corresponds to a gradual change in performance as a function of the target location.

The two-parametric cumulative Gaussian model has difficulties representing cancellation data if there is a sudden change in performance across space. This is illustrated in Figure 1, where we show data (dots) drawn from a model that represents a sudden large change in Figure 1A and data drawn from a model representing a sudden small change in Figure 1B. The line represents the best fitting two-parametric cumulative Gaussian and one can see that the fit is not optimal.

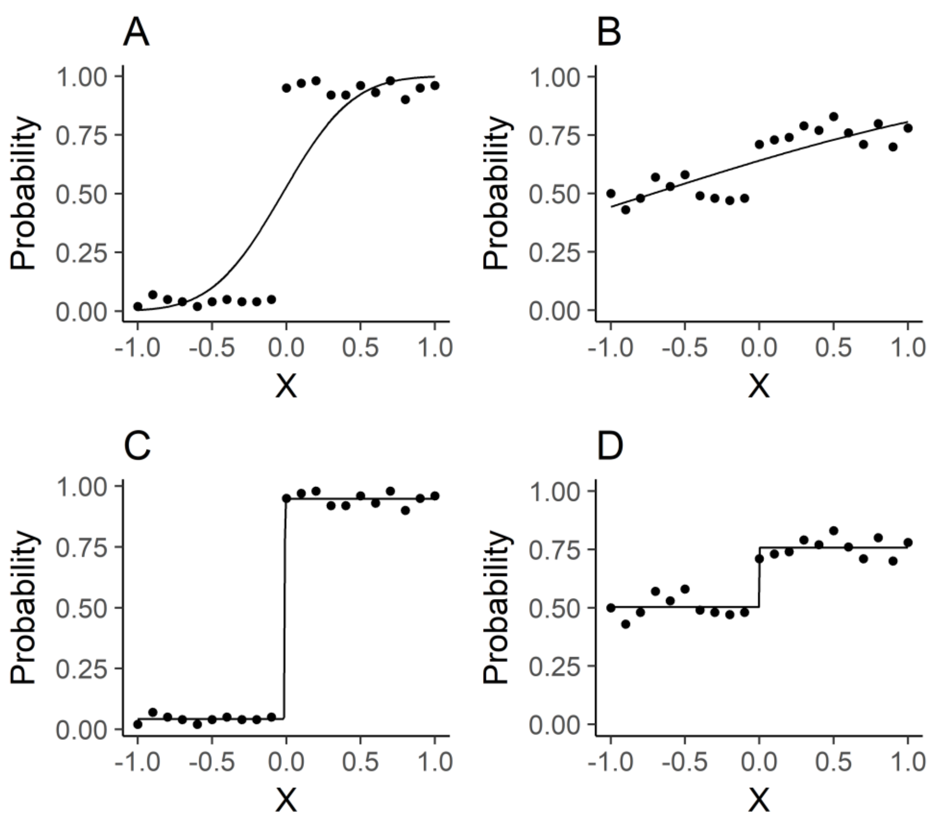

Figure 1. Data drawn from a step model and best fitting curves of a gradient model. Figure 1A and Figure 1B represent the best fitting curves for the two-parametric gradient model, while Figure 1C and Figure 1D represent the best fitting curves for the four-parametric model. If there is a sudden change in performance, the two-parametric model fits reasonably well (Figure 1A and Figure 1B), but the four-parametric model fits better (Figure 1C and Figure 1D).

To be able to represent sudden and gradual changes in performance, the cumulative Gaussian model can be extended by adding two parameters (Equation 1). A first parameter, ε, can be added to model the minimum probability to cancel a target. A second parameter, λ, can be added to model the maximum probability to cancel a target.

The gradient model is then formulated as follows:

Equation 1. $$f(x) = \varepsilon + (1 - \varepsilon - \lambda) \, . \left[\frac{1}{2}\left(1 + \operatorname{erf}(\frac{x - \mu}{\sigma\sqrt{2}})\right)\right],$$

where x stands for the target location, ε stands for the minimum probability to cancel a target, λ stands for the maximum probability to cancel a target, μ stands for the location of the inflection point, σ stands for the slope of the cumulative Gaussian function and erf stands for the Gauss error function, which is a special function of sigmoid shape.

In Figure 1C and Figure 1D we show data drawn from a model representing a sudden change in performance and the best fitting lines of the four-parametric cumulative Gaussian model. One can see that the model fit has drastically improved as compared to Figure 1A and Figure 1B by adding the two parameters. Thus, a four-parametric model is best able to represent different types of cancellation performance patterns, including gradual and sudden changes in performance.

Step 2. Inferring conceptually meaningful constructs from a gradient model

The gradient model can model one additional difference between patients as compared to the step model: the extent to which performance changes suddenly or gradually as a function of the target location. Figure 2 visualizes four examples of the four-parametric gradient model. Figures 2A and 2B represent gradual changes in performance across space, while Figure 2C and Figure 2D represent sudden changes in performance. Similar to the step model, the gradient model can represent the spatial asymmetry, neglected region and non-spatial errors (see Figure 2). However, we must note that the definition of the neglected region based on a gradient model is more arbitrary as compared to the step model. That is, as performance gradually changes as a function of the target location, there is no clear boundary between the neglected versus the non-neglected region of space.

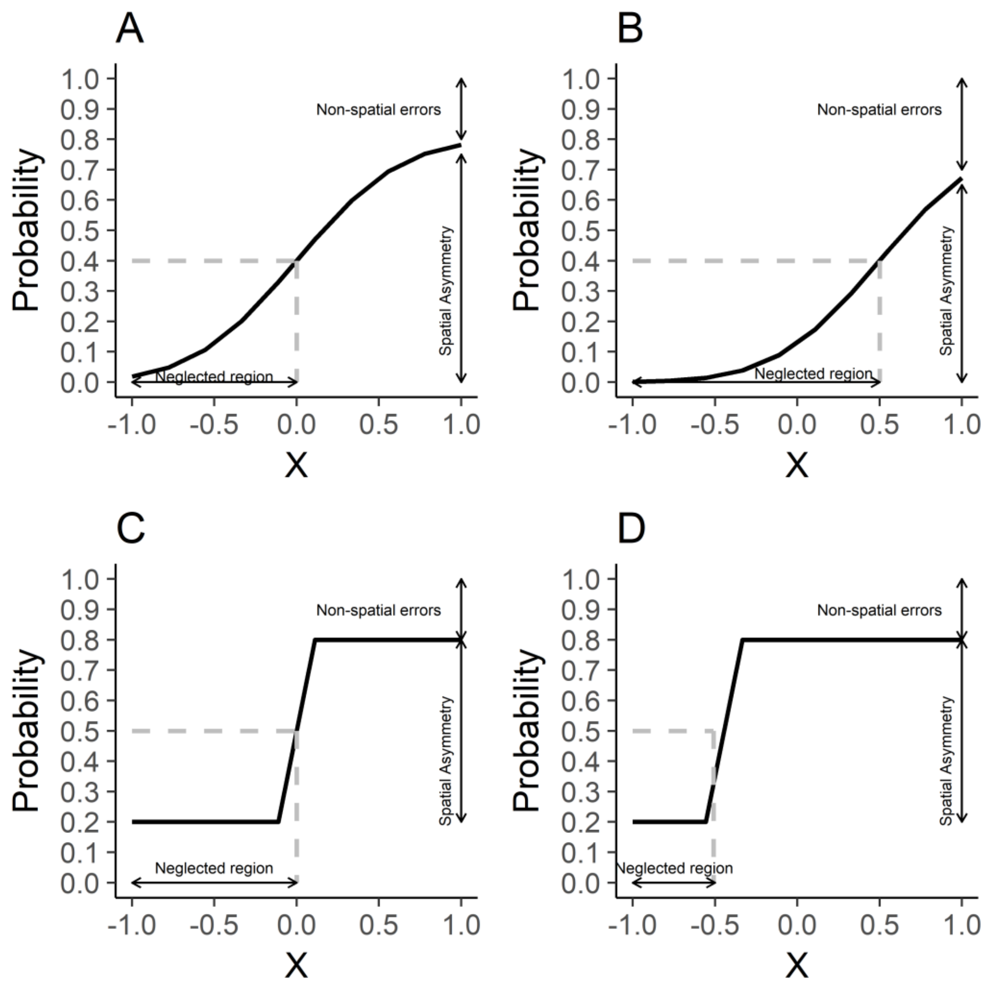

Figure 2. Four examples of the gradient model. On the x-axis the target location is depicted with -1 representing the left border, 0 representing the middle and 1 representing the right border of the cancellation display. On the y-axis the probability to cancel a target is displayed. Figure 1A displays a model with the following parameter values: . μ = 0, σ = 0.5, ε = 0 and λ = 0.20. Figure 1B displays a model with the same parameter values, except for μ being equal to 0.5. Figure 1C displays a model with the parameter values: μ = 0, σ = 0.01, ε = 0.20 and λ = 0.20. Figure 1D displays a model with the same values except for μ being equal to -0.5. In addition, the non-spatial errors, spatial asymmetry and neglected region corresponding to each model are depicted by the labeled arrows.

Step 3. Generating cancellation data

Simulated cancellation data were generated in the same way as described in the main text. Unless stated otherwise, we used the same procedure as explained in the main simulation analysis for these supplementary simulations.

In these simulations, the gradient model as described in Equation 1 was used to determine the probability to cancel a target. We chose to simulate data with a gradient model that either had a steep versus a shallow slope to represent the assumption that patients may vary in the extent to which their performance changes suddenly or gradually. Therefore, a σ of 0.01 and 0.50 was chosen. A σ of 0.50 was chosen as this corresponds to a Gaussian distribution of which the entire density can be located in the domain of target locations (going from -1 to 1). Thus, a distance of 2 units divided by 4 standard deviations resulted in a σ of 0.50. Parameter μ ranged from -1.5 to 1.5 in steps of 0.10 units. Parameters ε and λ both ranged from 0 to 1 in steps of 0.10 units. All combinations of these model parameters were used to generate fictional cancellation data with the restriction that the sum of parameters ε and λ could not exceed 1. The sum of parameters ε and λ cannot be larger than 1 as this would result in an expected probability larger than 1, which is impossible. For each unique model, 10,000 sets of cancellation data with 50 target locations and corresponding hits or misses were generated in the exact same way as for the step model simulations.

Based on the gradient model, the *spatial asymmetry* was defined as the difference between the probability to cancel a target at the two most extreme target locations on the cancellation display (max(f(x)) – min(f(x))). For left-sided neglect, the spatial asymmetry was multiplied with -1, so that negative values would correspond to left-sided neglect and positive values would correspond to right-sided neglect. The *non-spatial errors* were defined as the difference between the maximum possible probability to cancel a target minus the maximum achieved probability to cancel a target (1 – max(f(x)). The *neglected region* was defined as a function of the location of parameter μ. The area of space located on the side where the cumulative Gaussian function has a concave shape, is the neglected region, while the area of space located on the side where the cumulative Gaussian function has a convex shape is the non-neglected region (Figure 2). The neglected region ranges from 0 to 1. A neglected region of 0 means that only the convex part of the gradient model is located in the domain of target locations, while a neglected region of 1 means that only the concave part of the gradient model is located in the domain of target locations. A neglected region of 0.5 means that the inflection point is located in the middle of the cancellation page. However, we must note that, as the sigmoidal curve becomes less steep, the boundary between the neglected and non-neglected region becomes less clear.

Based on the simulated cancellation data, different measures of cancellation performance were calculated (see also main text). Thereafter, the average value of each measure of cancellation performance across the 10,000 iterations was calculated.

Step 4. Visualizing the data

Not all combinations of the neglected region and spatial asymmetry can be simulated when using a gradient model, because changing the location of the inflection point of the gradient model does not only affect the neglected region, but also affects the spatial asymmetry (Figure 2). Therefore, the parameter space is more restricted when simulating data with a gradient model as compared to with a step model. To make the results of the simulations comparable across models, we therefore restricted the parameter space of the step model simulations in the same way as for the gradient model simulations. That is, all combinations of the spatial asymmetry and neglected region that could not be simulated with the gradient model were left out of the contour plots of the step model.

Results

The results are visualized in Figure 3. For each cancellation performance measure, four contour plots are presented next to each other. The two contour plots on the left side of each row are the results of the simulation with the step model as described in the main text, but with the parameter space restricted in a similar way as the parameter space of the simulations based on the gradient model. The two contour plots on the right side of each row are the results of the simulation with the gradient model. In each set of two contour plots, the left-most contour plot represents the relationship between the cancellation performance measure (represented by the colours) on the one hand, and the spatial asymmetry and neglected region size on the other hand. For these contour plots the non-spatial errors are equal to 0. The rightmost contour plot of each set represents the relation of the cancellation performance measure (represented by the colours) to the spatial asymmetry and non-spatial errors. For these contour plots, the neglected region size has a constant value of 0.5.

For the first three cancellation performance measures, the total number of omissions (O, Figure 3A), the total number of contralesional omissions (NCO, Figure 3B) and the number of contralesional hits divided by the total hits (Con H / H, Figure 3C), we can see that each of these cancellation performance measures can have an extreme value (indicating spatial neglect) for situations in which there is no spatial asymmetry, but a high non-spatial error margin (red colours on the tip of the pyramid). This result is the same for the simulations based on the step model and gradient model.

None of the cancellation performance measures that directly compare performance between the left and right half of the cancellation display can have an extreme value when there is no spatial asymmetry (Figure 3D to Figure 3G). The L-R score (Figure 3D) depends on the spatial asymmetry, but not on the non-spatial errors both in the step model simulations and gradient model simulations. L-R does not represent the neglected region size properly and will underrepresent the spatial asymmetry if the neglected region extends into the ipsilesional side of space. This pattern is less pronounced for the gradient model, but remains present (the contours still follow a circular shape in the same direction as the contours in the step model results).

The contour plots of L-R / H (Figure 3E) and L/R (Figure 3F) show a dependency of these two cancellation performance measures on the non-spatial errors (the contours in the pyramid are not perpendicular to the y-axis). This pattern is also present in the results of the gradient model. Based on the step model simulations, we can conclude that the L-R / H score and L/R score cannot accurately reflect the spatial asymmetry when the neglected region extends into the ipsilesional side of space (for a constant spatial asymmetry, the values of L-R / H and L/R become smaller if the neglected region becomes larger). This pattern is highly similar for the simulation results of the gradient model.

For the CoC, the dependency on the non-spatial errors remains present for the step model and gradient model (Figure 3G). The CoC also shows a very similar dependency on the neglected region and spatial asymmetry for the step and gradient model.

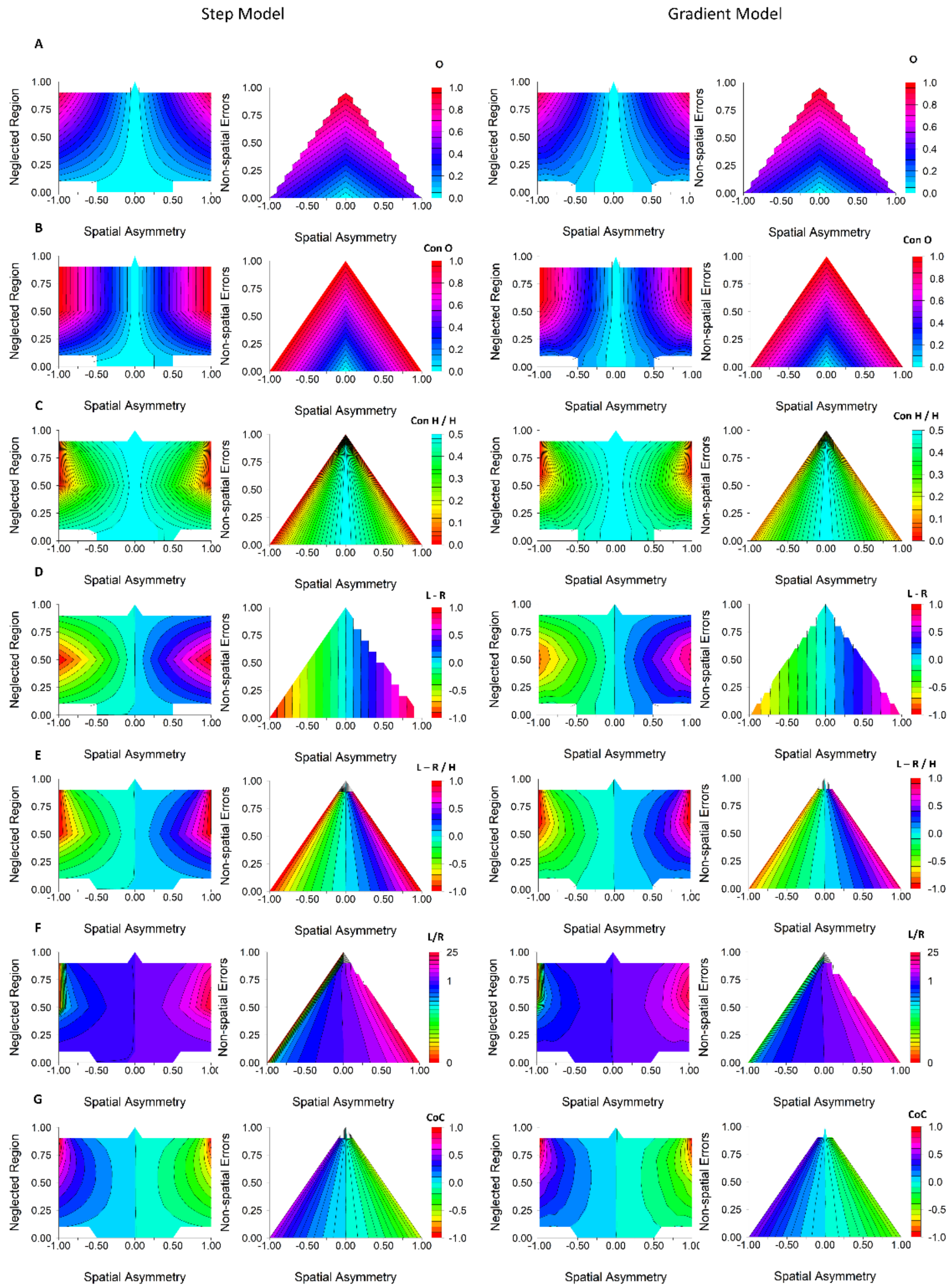

Figure 3. Contour plots of the cancellation performance measures. For each cancellation performance measure, four contour plots are presented next to each other. The two contour plots on the left side of each row are the results of the simulation with the step model as described in the main text, but with the parameter space restricted in a similar way as the parameter space of the simulations based on the gradient model. The two contour plots on the right side of each row are the results of the simulation with the gradient model. In each set of two contour plots, the leftmost contour plot represents the relation of the cancellation performance measure (represented by the colors) to the spatial asymmetry and neglected region size. For these contour plots the non-spatial errors are equal to 0. The rightmost contour plot of each set represents the relation

of the cancellation performance measure (represented by the colors) to the spatial asymmetry and non-spatial errors. For these contour plots, the neglected region size has a constant value of 0.5.

Discussion

As previous literature suggested that spatial neglect is characterized by a spatial gradient in performance (Chatterjee, Thompson, & Ricci, 1999; Dvorkin, Bogey, Harvey, & Patton, 2012; Karnath, 1994; Smania et al., 1998), one could question the extent to which the step model is a realistic model of cancellation performance. To address this concern, we tested whether the results depend on the use of a step model to simulate cancellation data. We formulated an alternative model, in which performance can gradually change as a function of the target location. For these supplementary simulations, we assumed that patients can vary in the extent to which their performance changes either gradually or suddenly across space. Using this gradient model, the results of the simulations are highly similar to the results of the step model. Thus, the extent to which performance changes suddenly for all patients or can change gradually for some patients does not impact the relationship between cancellation performance measures and the neglected region, spatial asymmetry and non-spatial errors.

References

Chatterjee, A., Thompson, K. A., & Ricci, R. (1999). Quantitative Analysis of Cancellation Tasks in Neglect. *Cortex*, *35*(2), 253–262. https://doi.org/10.1016/S0010-9452(08)70798-6

Dvorkin, A. Y., Bogey, R. A., Harvey, R. L., & Patton, J. L. (2012). Mapping the Neglected Space Gradients of Detection Revealed by Virtual Reality. *Neurorehabilitation and Neural Repair*, *26*(2), 120–131.

Karnath, H.-O. (1994). Disturbed coordinate transformation in the neural representation of space as the crucial mechanism leading to neglect. *Neuropsychological Rehabilitation*, *4*(2), 147–150.

Smania, N., Martini, M. C., Gambina, G., Tomelleri, G., Palamara, A., Natale, E., & Marzi, C. A. (1998). The spatial distribution of visual attention in hemineglect and extinction patients. *Brain*, *121*(9), 1759–1770. https://doi.org/10.1093/brain/121.9.1759

Wichmann, F. A., & Hill, N. J. (2001). The psychometric function: I. Fitting, sampling, and goodness of fit. *Perception & Psychophysics*, *63*(8), 1293–1313. https://doi.org/10.3758/BF03194544