Reduced effective connectivity between right parietal and inferior frontal cortex during audiospatial perception in neglect patients with a right-hemisphere lesion

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A B S T R A C T

A lesion to the right hemisphere of the brain in humans commonly leads to perceptual neglect of the left side of the sensorium. The clinical observation that lesions to disparate cortical and subcortical areas converge upon similar behavioural symptoms points to neglect as a dysconnection syndrome that may result from the disruption of a distributed network, rather than aberrant computations in any particular brain region. To test this hypothesis, we used Bayesian analysis of effective connectivity based on electroencephalographic recordings in ten patients (6 male, 4 female; age range 41–68) with left-sided neglect following a right-hemisphere lesion. In line with previous research, age-matched healthy controls showed a contralateral increase in connection strength between parietal and frontal cortex with respect to the laterality of audiospatial oddball stimuli. Neglect patients, however, showed a disconnection between parietal and frontal cortex in the right hemisphere when oddballs appeared on their left side, but preserved connectivity in the left hemisphere when stimuli appeared on their right. This preserved fronto-parietal connectivity was associated with lower neglect severity. Moreover, we saw ipsilateral fronto-temporal connectivity increases for oddballs appearing on the neglected side, which might be a compensatory mechanism for residual left side awareness. No group differences were found in intrinsic (within-region) connectivity. While further validation is required in a bigger sample, our findings are in keeping with the idea that neglect results from the disruption of a distributed network, rather than a lesion to any single brain region.

Significance statement

Lesions to the right hemisphere of the brain commonly lead to neglect syndrome, characterized by perceptual deficits where patients are unaware of the left side of their body and environment. Using analysis of non-invasive electrophysiological recordings, we provide evidence that patients with left-sided neglect have reduced connectivity between the right parietal and frontal cortex during audiospatial stimuli, but preserved connectivity between regions in the non-lesioned left hemisphere. Moreover, for these intact connections we observed an ipsilateral fronto-temporal increase in connectivity during oddballs appearing on the neglected side, which might be a compensatory mechanism for residual perception. Crucially, we found that patients with more severe neglect symptoms had reduced connectivity between parietal and frontal cortex in the left hemisphere. This suggests that neglect may be caused by the disruption of a distributed network in the brain, rather than a lesion to any particular brain region.

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1. Introduction

Neglect is one of the most common neurological disorders following stroke (Azouvi et al., 2002). Neglect patients are characterized based on the behavioural symptom that they ignore the side of the sensorium contralateral to a cortical or thalamoreticular lesion (Molenberghs et al., 2012). Importantly, neglect of the left side of the sensorium after a right-hemisphere lesion is more frequent and severe than neglect of the right hemisphere after a left-hemisphere lesion. This hemispheric asymmetry has been explained in terms of a right-hemisphere dominance of the fronto-parietal network that mediates attentional orienting to salient stimuli (Dietz et al., 2014). According to this hypothesis, a left-hemisphere circuit mediates attentional orienting to the right hemisphere, whereas the right hemisphere is involved in the orienting to both sides of the sensorium (Mesulam, 1999). There is a general heterogeneity in the lesion profiles of neglect patients (Molenberghs et al., 2012) and the observation that a lesion to temporal, frontal or parietal cortex leads to a similar perceptual deficit points to the notion of neglect as a disconnection syndrome (Lunven et al., 2015).

Two functional and anatomical systems have been proposed to underpin attentional processes: a dorsal fronto-parietal system for goal-directed deployment of attention and a ventral system for reorienting to salient or novel stimuli that appear unexpectedly in the sensorium (Corbetta and Shulman, 2011; 2002). While the dorsal system consists of the first and second branches of the superior longitudinal fasciculus, the ventral system connects the inferior fronto-parietal cortex with the inferior parietal lobule via the third branch of this fronto-parietal fascicle (de Schotten et al., 2011). Anatomical and behavioral evidence for a hemispheric asymmetry has been shown in healthy participants where the white matter volume of the third branch correlated with detection of targets in the left, but not the right visual field (de Schotten et al., 2011). Consistent with this relation between anatomy and behavior, neglect patients in the subacute phase show axonal degeneration in the second and third superior longitudinal fascicles of the right, but not the left hemisphere compared to stroke patients without neglect (Lunven et al., 2015). In the auditory system, we recently provided functional evidence for a right-hemisphere dominance in the effective (synaptic) connectivity between the inferior frontal gyrus and the inferior parietal cortex in healthy individuals during unexpected left and right auditory stimuli (Dietz et al., 2014). However, whether patients with left-sided neglect have reduced effective connectivity during audiospatial stimuli has not yet been investigated.

To this end, we recorded high-density electroencephalography (EEG) in patients (N = 10) with left-sided neglect following a right-hemisphere lesion and healthy age-matched controls (N = 11) during an auditory oddball paradigm where the location of the stimulus changed unpredictably to the left or the right side in egocentric coordinates. Using dynamic causal modeling (DCM) of evoked electrophysiological responses (David et al., 2006), we analyzed the strength of feedforward and feedback connections between the primary auditory cortex in Heschl’s gyrus (HG), the inferior frontal gyrus (IFG) and the inferior parietal lobule (IPL). Within this hierarchy of cortical regions, we then tested a set of alternative hypotheses about the laterality of the ventral system that mediates perception of salient stimuli. Our set of hypotheses represented (a) a contralateral encoding of the sensorium with respect to the side of the stimulus (b) a left-lateralized encoding of the sensorium and (c) a right-hemisphere dominant encoding (see Fig. 1 for a schematic of alternative hypotheses). The hypothesis of a contralateral increase in effective connectivity was motivated by the “contralateral bias” model (Kinsbourne, 1987). The hypothesis that patients may show a left-lateralized cortical network was based on their lesion profile in the right hemisphere that causes perceptual neglect of the left side of the sensorium. Finally, the hypothesis that the right hemisphere codes both sides of the sensorium was based on the right-hemisphere dominance model (Dietz et al., 2014; Mesulam, 1999).

2. Materials and methods

2.1. Patient data

We recorded EEG responses and behavioural data from 10 patients (average age 59, age range 41–68) with neglect of the left side of the sensorium during their subacute phase (Table 1). The control group was age-matched to the patient group to within 3 years and consisted of 11 healthy volunteers (average age 56, age range 44–71) with no history of neurological or psychiatric disorder. In this age-matching procedure, differences due to normal aging are assumed to be negligible, while preserving the random sampling of controls from the population. The patients had heterogeneous lesion profiles in the right cerebral hemisphere and the severity of contralateral neglect was classified according to the conventional part of the Behavioural Inattention Test (BIT-C) (Wilson et al., 1987). The BIT-C scale ranges from 0 to 146, where a lower score is taken as evidence of more severe neglect. All patients expressed neglect symptoms corresponding to a BIT-C score below 129 points at the time of EEG acquisition. Due to limited hospital admissions, it was practically impossible to recruit an ac-
tive control group consisting of patients with a right-hemisphere lesion, but without neglect. In fact, all patients who met our inclusion criteria also had a degree of neglect. Finally, to ensure the validity of EEG forward modeling, we only included patients who had not undergone craniotomy.

2.2. Experimental design

We recorded 64-channel electroencephalography (EEG) from patients and healthy controls using active Ag/AgCl electrodes placed according to the extended 10–20% system using channel FCz as reference (Brain Products, GmbH). Data were sampled at 1 kHz with a high-pass filter at 0.1 Hz and a low-pass filter at 450 Hz for anti-aliasing. Participants were presented with an auditory oddball paradigm where the location of a tone changed in an unpredictable fashion from the midline to the left or the right side in egocentric coordinates. Stimuli perceived as originating from the midline were repeated consequently between 3 and 7 times by randomly sampling from a deterministic multinomial distribution, thus occurring with 80% probability. An interaural time delay (ITD) of 800 μs between left and right ears was used to create a change in the location of the stimulus to the egocentric left and right side at approximately 90° angle in the horizontal plane. Stimuli at left and right locations each had 10% probability of occurrence. All other spectral, amplitude and duration parameters were kept constant. Stimuli consisted of sinusoidal pure tones with 75 ms duration, including 5 ms fade-in and 5 ms fade-out. We used Presentation software (Neurobehavioural Systems, Inc) to deliver stereo stimuli through in-ear headphones (Sennheiser, Gmbh) at a stimulus-onset asynchrony of 500 ms. The sound pressure level was manually adjusted to lie between the individual participants’ hearing threshold and their nuisance level. Each participant was presented with a total of 1800 stimuli (1440 midline, 180 left and 180 right). Participants were instructed to maintain fixation on a central cross (on a black screen) during the experiment. Patients and controls were monitored to make sure they kept their head still and did not fall asleep. Ethical approval was obtained from the local ethics committee of the Central Denmark Region, Denmark and patients and healthy controls gave their informed written consent before the experiment according to the Declaration of Helsinki.

2.3. EEG data analysis

Data analysis was performed using Statistical Parametric Mapping (SPM12) academic freeware implemented in Matlab (MathWorks Inc., USA). The EEG data were re-referenced to the average over channels, down-sampled from 1 kHz to 250 Hz, high-pass filtered at 0.5 Hz and low-pass filtered at 30 Hz using a two-pass Butterworth filter. Experimental trials were epoched from −100 to 400 ms in peri-stimulus time and baseline-corrected using the average over the pre-stimulus time-window. Artefacts were rejected by thresholding the signal at 80 μV, leaving on average 80% of trials for analysis. Trials were averaged within condition to form evoked responses. We used robust averaging, a form of robust general linear modeling (Wager et al., 2005), where the distribution of data over trials at each channel and time bin is used to down-weight outliers under Gaussian assumptions. We used the default setting of the weighting function in SPM, which preserves approximately 95% of the data. To enable an unbiased analysis in sensor space over post-stimulus time, the averaged data were converted into a spatiotemporal image consisting of a 2D sensor representation plus a temporal dimension, time-point by time-point, over post-stimulus time. 3D images were then smoothed with a Gaussian kernel of 20 mm full-width at half maximum (FWHM) in the spatial dimension and 20 ms in the temporal dimension. The results were thresholded at p < 0.05, corrected for the family-wise error (FWE) rate using random field theory in space and time (Kilner and Friston, 2010).

2.4. Specification of alternative hypotheses as alternative dynamic causal models

We specified a set of dynamic causal models that describe the effective connectivity between temporal, frontal and parietal areas, based on known functional anatomy. In contrast to previous studies that included both primary auditory cortex (A1) and the superior temporal gyrus (STG) (Aukstulewicz and Friston, 2015; Cooray et al., 2014; 2016; Dietz et al., 2014; Garrido et al., 2008; 2009; 2007), we simplified the network using Heschl’s gyrus (HG) as the temporal source. Given the anatomical proximity of A1 and STG, modeling both sources could become redundant in the present context, where our hypotheses concerned stimulus-specific changes and syndrome-specific differences in the extrinsic connectivity between temporal, frontal and parietal regions.

These models tested a set of alternative hypotheses about the laterality of the cortical mechanisms that mediate the perception of a stimulus in a new spatial location. Our alternative hypotheses represented a contralateral increase in the strength of effective connectivity with respect to the side of the stimulus (model C), a left-lateralization in effective connectivity (model L) and a right-hemisphere dominance (model R). Following our previous study in healthy individuals (Dietz et al., 2014), we used existing anatomical knowledge to set the prior mean of the dipole locations - used to summarize each cortical area - to the following coordinates in MNI space: left [-42 –22 7] and right [46 –14 8] Heschl’s gyrus (HG), left [-46 28 8] and right [46 28 8] inferior frontal gyrus (IFG), as well as left [-49 –38 38] and right [57 –38 42] inferior parietal cortex (IPC). This cortical network received feedforward input to bilateral HG, assumed to arrive from the medial geniculate body of the thalamus (Kass and Hackett, 2000). This was modelled as a Gaussian impulse with a prior mean of 60 ms and prior standard deviation of 16 ms. The primary auditory areas
on the superior temporal plane connected to the inferior frontal gyrus (Romanski et al., 1999) which connected to the inferior parietal cortex via (extrinsic) feedforward and feedback connections in keeping with anatomical knowledge of the superior longitudinal fasciculus (de Schotten et al., 2011). We modelled the data during the post-stimulus period 0–350 ms. This period encompasses components of the evoked response that are assumed to reflect the detection of a change in the stimulus location (Dietz et al., 2014) and a subsequent bottom-up attentional reorienting to the left or the right hemispace.

2.5. Dynamic causal modeling of evoked EEG responses

Dynamic causal modeling (DCM) is a method for estimating the directed coupling between brain regions and how this coupling changes with stimulus or behavioural context. We used a biologically realistic neural-mass model (David et al., 2006) that summarizes the dynamics, within an electromagnetic source, as the average post-synaptic membrane depolarization of four cell populations whose intrinsic (vertical) connectivity conforms to a canonical corticocortical circuitry (CMC) (Bastos et al., 2012). This CMC model comprises (i) a population of excitatory spiny stellate cells that is the target of feedforward input from another anatomical region, (ii) a population of inhibitory interneurons whose connectivity is confined to the cortical patch and (iii) distinct populations of excitatory pyramidal cells in deep and superficial layers that are the sources of extrinsic feedback and feedforward connections between regions or patches of cortex, respectively (see Fig. 3g for a schematic of the CMC model). DCM is parameterized with a log-scaling parameter on its intrinsic and extrinsic connections to provide posterior estimates of the connection strengths and their context-dependent changes, given electrophysiological data. This renders DCM a generative model that operates at the level of the biophysical parameters that cause neuronal dynamics, as opposed to metrics of functional connectivity that operate at the (phenomenological) level of observed data features, such as coherence, phase-locking or Granger causality.

The observation model, mapping from biophysical parameters to predicted EEG responses, consisted of a spatiotemporal formulation of a conventional equivalent current dipole (ECD) forward model. This models the observed channel data as a mixture of post-synaptic membrane depolarization and additive Gaussian noise. Each source in the network was modelled as a dipole whose locations and orientations parameterize the electromagnetic lead-field that describes the spatial mapping from average post-synaptic membrane potential to observed EEG data, assuming additive Gaussian measurement noise. This lead field was based on a boundary element method (BEM) head model to describe the propagation of the electrical current through the tissues and skull onto the scalp surface (Mosher et al., 1999). This forward model assumes normal volume conductance of the electrical current through the tissue and cranial layers when predicting the observed scalp topography.

The accuracy of EEG source localization is sensitive to violations of realistic conductivities of the brain, skull, and scalp in the forward model (Leahy et al., 1998). In particular, holes in the skull following craniotomy are known to substantially alter volume conductance properties and hence violate the assumptions of forward models based on normal head geometry (Oostenveld and Oostendorp, 2002; Wolters et al., 2006). Among the tissue types used in a standard Boundary Element Method (BEM) head model, the skull is thought to have the largest effect on observed electric fields because of its low conductance (Stenroos and Hauk, 2013). For this reason, we did not include patients who had undergone craniotomy and hence the standard conductivities for skull and scalp should not be violated in our patients. While the conductivity of the brain, cerebrospinal fluid and meninges may be altered depending on lesion etiology (Vatta et al., 2002), there is evidence that EEG source localization is robust to brain lesions. A study in epileptic patients with large lesions showed excellent source localization accuracy within the epileptogenic zone, comparable to the localization accuracy of epileptogenic foci in patients without a lesion (Brodebeck et al., 2009). In our study, whether a dipole was placed exactly in a damaged area is unknown, given the lack of anatomical images. However, the variational Bayesian ECD source estimation scheme used here allowed the location (and orientation) of each dipole to be optimized in the vicinity of its prior mean location, bounded by its prior variance. In other words, if a dipole is placed a priori in a damaged part of cortex that does not generate stimulus-related post-synaptic responses, it is free to move to a location within its vicinity that better explains the observed EEG responses.

2.6. Bayesian model comparison

Dynamic causal models are estimated using variational Laplace (Friston et al., 2007). This provides both the posterior distribution of the connection strengths and the marginal likelihood of the model itself, also known as the model evidence. Using a Laplace approximation to the multivariate posterior distribution of the model parameters \( q(\theta | y, m) \), the conditional means and covariances are estimated iteratively by maximizing a lower bound on the logarithm of the model evidence \( \ln p(y|m) \), henceforth log-evidence. This optimization uses Newton’s method and a Fisher scoring scheme to maximize the (negative) variational free-energy \( F_o \) of the model

\[
F = E_q[\ln p(y|\theta, m)] - D_{KL}(q(\theta | y, m) \parallel p(\theta | m))
\]

where \( E_q[\cdot] \) denotes the expectation under the variational posterior density \( q(\theta | y, m) \) and \( D_{KL}(\cdot | \cdot) \) is the relative entropy or Kullback-Leibner divergence. This renders the free energy a lower-bound approximation to the log-evidence. To understand why the free energy is a useful for model comparison, we can decompose it into two terms. The first term is the expected log-likelihood of data \( y \) and represents the accuracy of the model. The second term is the relative entropy or Kullback-Leibner (KL) divergence between the multivariate posterior and prior probability densities and represents the complexity of the model. The formulation of the complexity as a KL divergence rests on the assumption that the posterior should not have to move too far from the prior to accommodate the data. In other words, a good model should provide posterior beliefs that are consistent with its prior beliefs after observing new data. The free energy can thus be decomposed into accuracy minus complexity. Together, these two terms summarize the quality of a model in explaining the data. Our set of alternative hypotheses (DCMs) were then compared using their free energy (Penny, 2012). We used a random-effects Bayesian model selection (RFX BMS) procedure to provide the posterior probability and protected exceedance probability of each model for model comparison within each population (Penny et al., 2010). The protected exceedence probability was recently introduced in the statistical literature in the context of Bayesian model selection to quantify the posterior probability that a model is more frequent in the sample than the other models in the comparison set, above and beyond differences in model frequencies that are expected to occur by chance (Rigoux et al., 2014).

3. Results

3.1. Evoked responses in healthy participants

We first tested for cortical responses evoked by salient left and right stimuli in healthy participants using one-sample t-tests
Evoked cortical responses in healthy participants and neglect patients (a) Evoked responses to midline, left and right stimuli in healthy participants (b) Scalp topography of the P3a induced by left stimuli at 260 ms post-stimulus time (c) Scalp topography of the P3a induced by right stimuli at 276 ms post-stimulus time (d) Evoked responses to midline, left and right stimuli in neglect patients (e) Scalp topography induced by stimuli on the patients’ neglected side at 292 ms post-stimulus time (f) Scalp topography of the P3a induced by right stimuli at 292 ms post-stimulus time (g) Statistical t-map of the difference between healthy participants and neglect patients during left stimuli with a peak at 240 ms post-stimulus time (h) Average responses and 95% confidence intervals in healthy participants and neglect patients at the peak of the parieto-central cluster identified in (g) above.

Fig. 2. Evoked cortical responses in healthy participants and neglect patients (a) Evoked responses to midline, left and right stimuli at 260 ms post-stimulus time (b) Scalp topography of the P3a induced by left stimuli at 276 ms post-stimulus time (c) Scalp topography of the P3a induced by right stimuli at 292 ms post-stimulus time (d) Evoked responses to midline, left and right stimuli in neglect patients (e) Scalp topography induced by stimuli on the patients’ neglected side at 292 ms post-stimulus time (f) Scalp topography of the P3a induced by right stimuli at 292 ms post-stimulus time (g) Statistical t-map of the difference between healthy participants and neglect patients during left stimuli with a peak at 240 ms post-stimulus time (h) Average responses and 95% confidence intervals in healthy participants and neglect patients at the peak of the parieto-central cluster identified in (g) above.

at the group level, family-wise error (FWE) corrected for multiple comparisons in space and time using random field theory at the peak level (Kilner and Friston, 2010). This analysis revealed evoked responses over the fronto-central scalp to both left and right stimuli, relative to stimuli presented in the midline (Fig. 2a) which resemble the typical mismatch negativity (MMN) observed in oddball paradigms. These responses peaked at 164 ms for the left ($t_{10} = 9.89, P = 0.003$, FWE-corrected one-sample t-test) and at 176 ms for the right stimulus ($t_{10} = 7.39, P = 0.005$, FWE-corrected one-sample t-test). Later in post-stimulus time, we observed a response over the parieto-central scalp, evoked by left and right deviancy with a peak at 260 ms for the left ($t_{10} = 4.5, P = 0.001$, FWE-corrected one-sample t-test, Fig. 2b) and a peak at 276 ms for the right stimulus ($t_{10} = 2.89, P = 0.009$, FWE-corrected one-sample t-test, Fig. 2c). We interpret this response as a P3a given its peak latency and topography, characteristic of oddball paradigms that typically induce reorienting of attention to salient stimuli (Polich, 2007).

3.2. Evoked responses in neglect patients

Having observed a typical MMN and P3a in healthy controls, we then tested for cortical responses evoked by salient left and right stimuli in neglect patients using a one-sample t-test at the group level, family-wise error (FWE) corrected for multiple comparisons in space and time using random field theory at the peak level. This revealed evoked responses to both left and right stimuli, relative to midline stimuli (Fig. 2d) that again resembled a MMN with a peak at 128 ms for the left ($t_{9} = 4.87, P = 0.007$, FWE-corrected one-sample t-test) and a peak at 156 ms for the right stimulus ($t_{9} = 5.72, P = 0.04$, FWE-corrected one-sample t-test). We then tested for responses later in post-stimulus time and observed an evoked response when salient stimuli appeared on the patients’ right side, with a peak at 292 ms ($t_{9} = 2.25, P = 0.02$, FWE-corrected one-sample t-test, Fig. 2e). Again, we interpret this response as a P3a, which is known to reflect attentional reorienting to salient or unexpected stimuli in healthy participants (Polich, 2007). However, when stimuli appeared on the left (neglected) side, we failed to detect a typical P3a (Fig. 2e). We then tested for a difference in evoked responses between patients and controls during left and right deviancy. This revealed a group difference during left deviants over the parieto-central scalp with a peak at 240 ms ($t_{9} = 4.88, P = 0.02$, see Fig. 2g and 2h). This difference in evoked activity lies within in the typical P300 latency range. We did not observe a group difference for right deviancy.
3.3. Bayesian analysis of effective connectivity

Following our previous study in neurotypical participants (Dietz et al., 2014), we analyzed a cortical network consisting of bilateral Heschl’s gyrus (HG), bilateral inferior frontal gyrus (IFG), and bilateral inferior parietal cortex (IPC). We analyzed the connection strengths in each hemisphere for each patient and control during salient left and right stimuli, relative to the midline. In addition to the extrinsic connections, we also analyzed the intrinsic connectivity within each cortical source. Using Bayesian model selection, we then compared the log-evidences for our alternative hypotheses: (a) contralateral encoding (b) left-lateralised encoding and (c) right-dominant encoding in patients and controls, separately. This allowed us to identify distinct network architectures for patients and controls under the assumption that patients use a reduced cortical network due to their right-hemisphere lesion.

3.4. Right-dominant network in the typical brain

Consistent with previous results in healthy younger adults (aged 20–35 years) (Dietz et al., 2014), the healthy controls (aged 44–71 years) showed a right-hemisphere dominance in the effective connectivity between temporal, frontal and parietal cortex (Protected exceedance probability $P > 0.88$, Fig. 3a). The qualification of right-hemisphere dominance is provided by the Bayesian model comparison of our three alternative dynamic causal models (contralateral, left-lateralized and right-dominant) fitted to all conditions (left and right deviancy, relative to standards). This is a qualification based on inference at the model level using model evidence, as opposed to inference on single parameters.

We then tested for a significant increase in connection strengths within this hierarchical network during left and right salient stimuli. An increase in connection strength corresponds to an increase in post-synaptic efficacy or the influence of an ax-
onal projection on its post-synaptic target population. This analysis revealed that (Fig. 3c), when salient stimuli appeared on the left, there was an increase in feedforward connection strength from right IFG to IPL \((t_{10} = 3.3, P = 0.004, \text{one-sample } t\text{-test, Bonferroni-corrected for number of connections})\). This feedforward influence was reciprocated by an increase in feedback connection strength from right IPL to IFG \((t_{10} = 2.9, P = 0.007, \text{one-sample } t\text{-test, Bonferroni-corrected})\) and an increase in feedback connection strength from right IFG to HG \((t_{10} = 2.9, P = 0.007, \text{one-sample } t\text{-test, Bonferroni-corrected})\). In contrast, when salient stimuli appeared on the right, there was an increase in feedforward connection strength from left IPL to IFG \((t_{10} = 2.2, P = 0.02, \text{one-sample } t\text{-test})\) and an increase in feedback connection strength from left IPL to HG \((t_{10} = 2.1, P = 0.03, \text{one-sample } t\text{-test})\). Finally, there was an increase in the feedback connection strength from IFG to HG in the right hemisphere \((t_{10} = 1.9, P = 0.03, \text{one-sample } t\text{-test})\). In other words, when stimuli appeared on the left or the right side in egocentric coordinates, there was an increase in the strength of feedforward and feedback connectivity in the hemisphere contralateral to the side of stimulation, with an additional feedback influence in the right hemisphere when stimuli appeared on the right. This replicates our earlier findings in the younger adult brain that showed a similar contralateral encoding of stimulus laterality within a right-dominant network (Dietz et al., 2014). As a complement to Bayesian model comparison, we assessed the accuracy of the optimal model in explaining the observed data in terms of the difference between the model’s predicted responses and the observed electrophysiological responses. This showed that the right-dominant DCM explained, on average, 59% of the variance in the healthy controls.

3.5. Left-lateralized network in neglect patients

Bayesian model selection revealed that evoked EEG responses in neglect patients were best explained by the left-lateralized encoding model (Protected exceedance probability \(P > 0.95, \text{Fig. 3d}\)). The qualification of left-lateralization is provided by the Bayesian model comparison of our three alternative dynamic causal models. A Bayesian omnibus risk (BOR) of \(P < 0.0001\) provides further evidence that a left-lateralized network of effective connectivity was consistent across patients. The BOR is a measure of the statistical risk incurred by performing Bayesian model comparison at the group level, where different patients may use different connectivity architectures. Alongside the protected exceedance probability of \(P > 0.95\) for the left-lateralized encoding model, the BOR of \(P < 0.0001\) is the posterior probability that this result occurred by chance in our sample of patients (Rigoux et al., 2014). This is entirely consistent with the patients’ lesion profiles that were all restricted to the right hemisphere. We then tested for significant changes in connection strengths within this left-hemispheric network. This revealed that, when salient stimuli appeared on the patients’ right side, there was an increase in feedback connection strength from left IPL to IFG \((t_{10} = 2.4, P = 0.01, \text{one-sample } t\text{-test, Bonferroni-corrected})\). This is analogous to the corresponding homotopic connection in the healthy controls and is consistent with the patients’ preserved perception of the right side of the sensorium. In contrast, when the stimuli appeared on their left side, there was an increase in feedback connection strength from left IFG to HG \((t_{10} = 1.96, P = 0.04, \text{one-sample } t\text{-test})\), indicating perhaps a compensatory mechanism for ipsilateral encoding (unseen in the healthy controls).

3.6. Patients with more severe symptoms have weaker feedback connectivity

We then tested for a relationship between the patients’ individual differences in neglect severity, as expressed by their BIT-C score (Table 1), and the strength of cortical connections in response to stimuli on the patients’ (neglected) left side. This revealed that patients with more severe symptoms had weaker feedback connectivity from the left IPL to IFG \((t_{10} = 3.09, P = 0.007, \text{linear regression, Bonferroni-corrected for the number connections})\). While caution is required when interpreting linear regression with a relatively small sample size, this finding suggests that neglect severity is associated with reduced top-down parieto-frontal connectivity. Note that stronger neglect symptoms correspond to a lower BIT-C score (Fig. 3f). In contrast, there was no evidence of such a relation between neglect severity and the strength of intrinsic connections within temporal, frontal or parietal areas (data and parameters not shown). Again, we assessed the accuracy of the optimal model in explaining the observed data in terms of the difference between the model’s predicted responses and the observed electrophysiological responses. This showed that the left-lateralized DCM explained, on average, 64% of the variance in the patients’ data.

3.7. Disconnection of right parietal and frontal cortex in neglect patients

Having identified a left-lateralized network in neglect patients and a right-dominant network in the healthy subjects, we then tested for a difference in both extrinsic (cortico-cortical) and intrinsic (intra-cortical) connection strengths between the patients and the controls in both hemispheres. This was done using Bayesian model averaging (BMA) obtained by weighting the average of each connection strength, within each subject, in relation to the posterior probability of each alternative model (Hoeting et al., 1999; Penny et al., 2010). This BMA effectively removes uncertainty about model structure and allows us to compare connection strengths between patients and healthy controls that use different networks in the brain. This revealed that when stimuli appeared on their neglected (left) side, patients had weaker feedback connectivity from right IPL to IFG \((t_{10} = 2.04, P = 0.02, \text{two-sample } t\text{-test})\), weaker feedforward connectivity from right IFG to IPL \((t_{10} = 1.89, P = 0.03, \text{two-sample } t\text{-test})\) and weaker feedback connectivity from right IFG to HG \((t_{10} = 1.97, P = 0.03, \text{two-sample } t\text{-test})\) compared to the age-matched healthy controls (see Fig. 4c for a schematic of the disconnections). This finding is evidence of impaired recurrent processing in the right hemisphere of neglect patients compared to healthy controls when stimuli appeared on their left side. In contrast, there was no evidence of a difference in connection strengths between patients and controls when stimuli appeared on their right side (significance criterion \(P < 0.05, \text{two-sample } t\text{-test})\). Likewise, there was no evidence of a difference in the intrinsic connectivity between patients and controls (significance criterion \(P < 0.05, \text{two-sample } t\text{-test, Fig. 4b}\)).

4. Discussion

In this study, we tested alternative hypotheses about the brain connectivity that mediates the encoding of stimuli in neglect patients and age-matched controls. In contrast to healthy controls who engage a right-dominant network, patients with neglect engage a left-lateralized network. This putative compensation mechanism is unsurprising given that their lesion profile is restricted to cortical lesions in the right hemisphere. In keeping with the
Group differences in effective connectivity between neglect patients and healthy controls

![Diagram showing canonical microcircuit model (CMC) and intrinsic connectivity (group differences)](image)

**Fig. 4.** Group differences in effective connectivity (a) Canonical cortical microcircuit (CMC) model used to estimate the intrinsic and extrinsic connectivity within and between cortical sources, respectively. The CMC is a neural mass model comprising a population of spiny stellate (SS) cells, a layer-wide population of inhibitory interneurons (II) and distinct populations of deep pyramidal (DP) neurons in layers 5/6 and superficial pyramidal (SP) cells in layers 2/3 that interact to generate feedforward and feedback output (b). No group differences were observed in intrinsic connections within temporal, frontal, and parietal areas (c) Right hemispheric fronto-temporal and fronto-parietal dysconnection in for oddballs on the left side of the sensorium. Average connection strength and 95% confidence intervals for the feedback connection from right IPL to IFG, the feedforward connection from IFG to IPL, and the feedback connection from IFG to HG, all showing weaker connection strengths in patients compared to healthy controls.

dysconnection hypothesis for neglect (Corbetta and Shulman, 2011; Dietz et al., 2014; He et al., 2007), we specifically show that neglect patients present with a dysconnection between parietal, frontal, and temporal regions in the right hemisphere. In the left hemisphere, on the other hand, the effective connectivity was preserved. Here we identify an ipsilateral increase in fronto-temporal connectivity during stimuli on the neglected side, which might be a compensatory mechanism for residual awareness to the left side and an increase in fronto-parietal connectivity in patients with less severe neglect symptoms. In healthy age-matched controls, we show a contralateral increase in connection strengths with respect to stimulus laterality between parietal, frontal, and temporal regions. This replicates our previous work in younger healthy adults under the same experimental paradigm (Dietz et al., 2014).

Previous studies of electrophysiological responses in neglect have shown abnormal ERPs to both visual and auditory stimuli. In particular, the reduced P3a during left visual target stimuli reported by (Lasaponara et al., 2018) is entirely in line with our result of reduced P3a in the auditory system. In contrast, we did not replicate the reduced MMN in neglect patients during left compared to right auditory stimuli reported by (Deouell et al., 2000), nor did we see a difference in MMN between patients and controls. Finally, the electrophysiological dysconnection reported here is entirely consistent with the disruption of the same fronto-parietal network measured with fMRI functional connectivity by (He et al., 2007).

**4.1. Active inference and failures of covert sampling**

Computational theories of the brain that describe neuronal connections as a process of Bayesian inference are becoming more and more useful for a mechanistic understanding of perception and action (Friston, 2010). We here provide an account of right-hemisphere dysconnection in terms of impaired precision within a generative model of the environment during covert sampling of left-sided stimuli, relative to the normal sampling of right-sided stimuli. This is related to the idea of mental action proposed by (Limanowski and Friston, 2018). In predictive coding, perception corresponds to inferring the hidden states in the world that cause sensations on our sensory epithelia. These states are hidden in the sense that the world can only be observed through noisy sensory data that change over time. In order to infer the states that cause sensory observations, such as an object in visual or auditory space, the brain must have a generative model that combines prior beliefs about states (causes) with the likelihood of observations (consequences) to form posterior beliefs (percepts). These probabilistic beliefs are encoded in terms of their expectation and precision. Precision is simply the inverse variance or uncertainty with which the brain represents the world. It follows from the form of this generative model that the brain must minimize the surprise – ln p(θ|m) about observations θ at any one time, given a particular model m or explanation of the world. However, computing surprise itself is mathematically intractable as it requires integrat-
ing over states \( s \) of the generative model. Using Jensen’s inequality, a plausible solution is that the brain minimizes an upper bound on surprise, known as variational free energy (Feynman, 1972; Friston, 2010)

\[
\ln p(\tilde{\mathcal{D}}) = -\ln \int p(\tilde{\mathcal{D}}, s) \frac{q(s)}{q(\tilde{\mathcal{D}})} \leq -\int q(s) \ln \frac{p(\tilde{\mathcal{D}}, s)}{q(s)} = \mathcal{F}
\]

Jensen’s inequality

where \( p(\tilde{\mathcal{D}}, s) \) is the joint likelihood of sensory observations and their hidden states, and \( q(s) \) is the approximate posterior probability density over states. These posterior beliefs are Bayes-optimal because they combine prior beliefs with new sensory data. This means an agent can update its posterior beliefs about the world in two ways. It can either update its prior beliefs about states based on current observations or it can actively sample new observations to reduce its uncertainty about states (Friston et al., 2017). In other words, perception and action go hand in hand to reduce uncertainty by jointly minimizing variational free energy. This is known as active inference. A key imperative of active inference is therefore to reduce uncertainty within a generative model of the world by actively sampling parts of the environment that require sensory interrogation (Parr and Friston, 2018; Schwartenbeck et al., 2019).

Unlike eye movements that mediate overt attention in the visual system, the auditory system can only make use of covert attention. Under recent computational theories of visual (Feldman and Friston, 2010) and auditory attention (Aukstsztulewicz and Friston, 2015; Dietz et al., 2014), this is achieved by the deployment of feedback or modulatory connections to increase the precision of sensory prediction errors at lower levels. This top-down deployment corresponds to active sampling of novel or salient stimuli that require sensory interrogation in order to reduce uncertainty about their identity or location, like the spatial oddball stimuli in our experiment. There is a fair amount of evidence that the ventral attention system is right-hemisphere dominant (Corbetta and Shulman, 2011; 2002; Dietz et al., 2014; Parr and Friston, 2018; Vossel et al., 2014). In this context, the posterior parietal cortex may have a generative model of space where each hemisphere encodes the contralateral side in egocentric coordinates (Andersen, 1997; Colby and Goldberg, 1999). Under active inference, a lesion critical to this ventral fronto-parietal network will lead to impaired precision at higher levels of the patient’s generative model of the environment. In the presence of a novel stimulus, this impairment of the precision at deeper levels of the model will then result in a Bayes-optimal failure of covert sampling of left-sided stimuli, relative to right-sided stimuli. Neurobiologically, this will be reflected in a decrease in feedback or modulatory connections. Traditionally, this is known as diaschisis where confined lesions in one part of the brain cause distal changes in synaptic efficacy and decreased metabolism (Carrera and Tononi, 2014). This is entirely consistent with our finding that subacute neglect patients have weaker feedback connectivity than healthy controls within the ventral fronto-parietal network. Indeed, this is in agreement with behavioural evidence of an general impairment of representational updating in neglect syndrome (Danckert et al., 2012).

4.2. Limitations and future directions

Our study is based on a very small sample size of patients with left neglect, which undoubtedly pose limitations on the generalizability of our findings that relate to both group differences (neglect versus healthy), and the association between neglect severity and connectivity. Unfortunately, the recruitment of neglect patients is extremely difficult and we suggest that coordinated efforts between multiple research hospitals are needed to achieve large cohorts. Another critical limitation speaks to the degree of specificity of our findings, in the absence of a control patient group with right hemisphere lesions but without neglect. If neglect patients willing to participate in research are a rare find, patients with similar lesions in the right hemisphere and without neglect are even rarer. Additionally, these patients often have other debilitating deficits that would in themselves be a confound. Indeed, it is extremely hard to equate patients on all parameters (e.g., lesion size and extent, neglect severity), hence another argument for the pressing need for bigger cohorts. Finally, we did not obtain access to MRI or CT images for research purposes, only a neurological description of each patient. While this was useful for a qualitative description of each patient’s lesion profile, it did not allow for a quantitative lesion mapping. Such a lesion map would be immensely useful for constraining the coupling parameters in DCM based on anatomically accurate lesion size and extent. For future studies, we will ensure that this information in available and combined with electrophysiological recordings.

4.3. Conclusion

We show that patients with a cortical lesion in the right hemisphere who present with left neglect impairments, have a functional disconnection between the right parietal and the frontal cortex. While further studies are required, including validation of our own in a much greater patient sample, our findings point to neglect as a disconnection syndrome whose etiology may lie in the disconnection of a distributed network, rather than the disruption of any single brain region.

Declaration of Competing Interest

The authors declare that there are no competing interests.

Credit authorship contribution statement

Martin J. Dietz: Conceptualization, Investigation, Project administration, Formal analysis, Software, Visualization, Writing - original draft, Writing - review & editing. Jørgen F. Nielsen: Conceptualization, Supervision, Resources. Andreas Roepstorff: Conceptualization, Supervision. Marta I. Garrido: Conceptualization, Supervision, Writing - review & editing.

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