Structural and effective brain connectivity underlying biological motion detection

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Abstract

The perception of actions underwrites a wide range of socio-cognitive functions. Previous neuroimaging and lesion studies have identified several components of the brain network for visual body motion (BM) processing, but interactions among these components and their relationship to behaviour remain little understood. Using a novel integrative analysis of structural and effective connectivity derived from high angular resolution diffusion imaging (HARDI) and functional magnetic resonance imaging (fMRI), we assessed the cerebro-cerebellar network for processing camouflaged point-light BM. Dynamic causal modelling (DCM) informed by probabilistic tractography indicated the right superior temporal sulcus (STS) served as an integrator within the temporal module. Furthermore, the prevalence of a structural pathway between the fusiform gyrus (FFG) and the STS was associated with better BM detection, and BM-specific effective connectivity from the FFG to STS predicted sensitivity to BM in a canonical variate analysis. However, the STS did not appear to be a 'gatekeeper' in the functional integration of occipito-temporal and frontal regions: the FFG and middle temporal cortex (MTC) were also connected to the right inferior frontal gyrus (IFG) and insula, indicating multiple parallel pathways. Furthermore, BM-specific loops of effective connectivity were seen between the left lateral cerebellar lobule Crus I and right STS, and between the left Crus I and right insula. A canonical variate analysis suggested that BM-specific changes in top-down connections from the IFG, insula and STS to the early visual cortex best predicted visual sensitivity to BM. Overall, the study characterises the architecture of the cerebro-cerebellar network for BM processing and offers novel perspectives for assessing the social brain.

Significance Statement

Visual perception of body motion is of substantial value for social cognition and everyday life. Using a novel integrative approach to brain connectivity, the study sheds light on architecture and functional principles of the underlying cerebro-cerebellar network. The circuity is organized in a parallel rather than hierarchical fashion. This may explain why body language reading is rather resilient to focal brain damage but severely affected in neuropsychiatric conditions with distributed network alterations. Furthermore, visual sensitivity to body motion is best predicted by specific top-down feedback to the early visual cortex, as well as functional communication (effective connectivity) and presence of white-matter pathways between the right fusiform gyrus and superior temporal sulcus. The findings allow better understanding of the social brain.

Introduction

Non-verbal social cognition (inferring the intentions, affective and mental states of others based on non-verbal information) predominates in our daily life (1-3). Understanding bodily signals represents a key element of social cognition (3-5). Perception of dynamic bodily signals is commonly assessed by point-light biological motion (BM; 6), as it enables one to separate the effects of motion from other attributes such as body shape or facial expressions (Supplementary Fig. 1). Innate tuning to body motion is seen across species (7, 8). Studies using different imaging modalities, such as functional magnetic resonance imaging (MRI), positron emission tomography (PET), electroencephalography (EEG) and magnetoencephalography (MEG) have unveiled components of the BM processing network. However, communication within this network remains little understood.

The main foci of reported activation are the superior temporal sulcus (STS; 9-19), fusiform gyrus (FFG; 16, 20-22), middle temporal cortex (MTC; 11, 20), parietal regions (10, 17, 21, 23), inferior frontal gyrus (IFG; 14, 24), bilateral insula (14, 25) and the left lateral cerebellum (26). More recently, using whole head ultra-high field 9.4T fMRI and temporal analysis of blood oxygen level dependent (BOLD) responses, distinct large-scale ensembles of regions (including early visual areas, the precuneus, several temporal and parietal regions, and the right IFG) have been reported to play in unison during different stages of BM processing (27).

The only task-related functional connectivity study of BM processing suggests the right FFG, MTC and STS are functionally integrated, and that the right STS exclusively entertains connectivity with the right insula and IFG (28). These findings may speak to a right temporal BM processing module comprising the FFG, MTC and STS. Furthermore, they imply a "gatekeeper" role for the STS receiving pre-processed information from the FFG and MTC but being the only region in communication with higher-order brain areas. This agrees with current conceptualisation of the STS as cornerstone of the BM processing network (3, 15). However,

the role of the FFG and MTC in BM processing remains unclear. The FFG exhibits strong responses not only to faces but also to static and dynamic bodies, leading to a designation of fusiform face and body areas (20, 29, 30). The MTC harbours both V5/MT+, crucial for global motion processing (31), and the extrastriate body area preferentially activated by bodies (32). Even the MTC sub-proportion clearly attributed to V5/MT+ is specifically tuned to static body parts as compared to objects (33).

Here, we assessed how BM processing modulates the causal interactions within the temporal module in order to infer a hierarchical connectivity among the FFG, MTC and STS. Second, we evaluated whether BM only modulates the FFG and MTC outputs to the STS (i.e., a "gatekeeper" architecture) or also their effective connectivity with other higher-order regions, thus indicating functional roles of the FFG and MTC beyond pre-processing for the STS. Finally, based on our recent findings (27, 34), we asked whether the early visual cortex receives BM-specific top-down modulation from higher-order regions.

We used dynamic causal modelling (DCM), the most established approach for effective connectivity analysis available for fMRI and M/EEG (35, 36). While functional connectivity (e.g., 28) between two regions may be inferred due to co-activation even in the absence of causal interactions, effective connectivity represents (causal) coupling among brain areas (37). Recent psychophysiological interactions (PPI) work in autism spectrum disorders (ASD) relates effective connectivity between the medial prefrontal cortex and right STS to visual sensitivity to BM (38) and effective connectivity between the STS and lateral cerebellum to social impairments (39). Both PPI and DCM allow one to assess the modulation of effective connectivity by context, but DCM additionally provides information on directionality (35). So far, only two DCM studies have addressed BM processing and were limited to specific connections: the right STS has been shown to entertain reciprocal effective connectivity with the left lateral cerebellar lobule Crus I (26) and the right FFG (40) in healthy adults. As inter-regional communication in the brain depends on connecting white-matter pathways, we

hypothesised our understanding of how BM is processed in the brain would benefit from a more comprehensive network characterisation that assimilates measures of white-matter connectivity afforded by HARDI with effective connectivity derived from fMRI, such as afforded by our previously developed structurally informed parametric empirical Bayes (si-PEB) method (41).

Our additional aim was to clarify whether, and if so, how, network connectivity can predict behavioural measures of performance. Most previous imaging studies have used canonical unmasked point-light BM displays that make the perceptual tasks relatively easy. Camouflaged BM, by affording reduced visual signal-to-noise ratio (Supplementary Fig. 1) rendered our BM task more demanding, thereby increasing variability in performance. The use of camouflaged BM in the present study enabled us to evaluate possible links between visual sensitivity to BM and network connectivity.

Results

Behaviour. Accuracy in recognition of presence and absence of the point-light walker (as percentage of correct responses) within an array of distractors was 90.3 % (range 71.7-100 %). Accordingly, the group d-prime as a measure of visual sensitivity to BM (42) was 3.64 ± 1.55 (range 1.15-6.43). The average hit rate (correct detection of walker-present trials) was 87.2 % (range 71.7-100 %).

fMRI Analysis. Whole-brain analysis of differential BOLD response for walker-present vs. walker-absent displays (represented by a positive parametric regressor in the general linear model (GLM); $p < 0.05$, FWE corrected; Fig. 1) revealed BM-specific effects in bilateral MTC (right: x = 46; y = -68; z = 0; left: x = -48; y = -70; z = -2; MNI coordinates), the right posterior STS (x = 50; y = -40; z = 10), FFG (x = 42; y = -56; z = -14), right anterior insula (x = 36; y = 24; z = 2), right IFG (x = 46; y = 10; z = 32) and the left cerebellar lobule Crus I (x = -36; y = -54; z = -28).

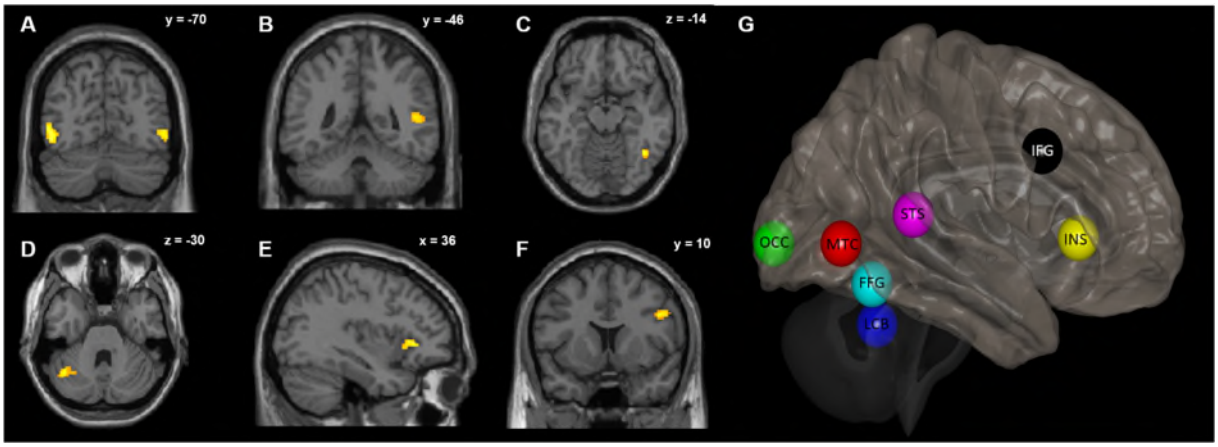

Fig. 1. Brain activity during perception of camouflaged BM. Regions showing higher BOLD responses for walker-present as compared to walker-absent displays ($p < 0.05$, family-wise error whole-brain corrected for multiple comparisons) are located in the (*A*) bilateral middle temporal cortices (MTC), (*B*) right superior temporal sulcus (STS), (*C*) right fusiform gyrus (FFG), (*D*) left lateral cerebellar lobule Crus I (LCB), (*E*) right anterior insula (INS) and (*F*) right inferior frontal gyrus (IFG). Activation clusters are overlaid on the MNI T1-template and slice positions in MNI space provided in the right upper corner. (*G*) Location of the seven network nodes (including early visual cortex, OCC) used in probabilistic tractography and dynamic causal modelling. These nodes are overlaid on a three-dimensional brain template.

Integration of Structural and Effective Connectivity. For analysis of effective connectivity, DCMs including the right FFG, MTC, STS, insula, IFG and the left lateral cerebellar lobule Crus I were created (see Methods and Fig. 1*G*). A region in the early visual cortex (OCC; x = 18; y = -94; z = 0) activated by the stimuli as compared to baseline ($p < 0.05$, FWE corrected) but not modulated by stimulus content was also included in order to provide a single, plausible entry point for the driving visual input.

Probabilistic tractography on the HARDI data returned the strengths of structural connections between these 7 network nodes with the same coordinates and radius. Subsequently, this structural connectivity was integrated in DCM constraining the group-level prior probability for the corresponding between-region effective connections in DCM. As the precise relationship between structural connection strength and prior probability can vary on a study-by-study basis (41), we created 405 different sigmoid mappings from structure to function defined by the hyperparameters α (intercept of the sigmoid), δ (sigmoid slope) and

$\Sigma_{y\,max}$ (maximum prior second-level probability) and used Bayesian model reduction (43) to select the model with the greatest evidence (i.e., marginal likelihood).

The log evidence of the optimal structurally informed model ($\alpha = 0$, $\delta = 4$ and $\Sigma_{y\,max} = 0.5$; Supplementary Fig. 2*B*) relative to the uninformed model was 3.43, corresponding to a 97 % posterior probability for the structurally informed model (with 'strong evidence' in favour of one model concluded at a posterior probability of 95 % or above: see 44). Direct structural pathways account for about two thirds of effective connections within this network; particularly in the temporal module (connectivity between MTC, FFG and STS; Supplementary Fig. 2*D*).

Using this optimal model afforded by the si-PEB procedure (41), we tested three specific hypotheses on how BM modulates effective connectivity within distinct parts of the network: (i) the temporal module (Supplementary Fig. 3), (ii) its connections to the inferior frontal gyrus and the insula (Supplementary Fig. 4) and (iii) top-down connections to visual cortex (Supplementary Fig. 5). All variants of models under each hypothesis (i.e., sets of connections showing BM effects) were specified in terms of prior constraints on modulatory effects of BM, yielding 1024 models. The evidence for the ensuing models was evaluated using Bayesian model reduction (43) within and between each set. Subsequently, Bayesian model averaging was used to estimate BM-sensitive changes in effective connectivity throughout the network.

Modulation of Effective Connectivity by Biological Motion in the Temporal Module. First, we asked which connections in the temporal module, and, in particular between the FFG on one side and the MTC and STS on the other, were selectively modulated by processing of camouflaged BM (Supplementary Fig. 3). Two equally probable models outperformed the remaining alternatives: model 12 ("only connections from the FFG to MTC and from the FFG to STS modulated by BM"; family-wise posterior probability 48 %) and model 11 ("only connection from the FFG to STS modulated by biological motion"; family-wise posterior probability 44 %). Given the pattern of extrinsic connectivity (Supplementary Fig. 2*C*), we can

thus infer an absence of effective connectivity from the STS and MTC to the FFG (Fig. 2*A*). Bayesian model averaging (followed by thresholding at a posterior probability of 95 % or above) indicated that BM processing does neither significantly modulate the ample baseline effective connection from the FFG to MTC – that is accompanied by a strong structural pathway (Supplementary Fig. 2*A*), nor the connection from the STS to MTC. In conclusion, these findings suggest the STS receives BM-specific afferents from both the FFG and MTC, without substantial BM-specific feedback from the STS or crosstalk between the FFG and MTC. This is consistent with an integrator role of the STS in the temporal module.

Interplay of the Temporal Module with Inferior Frontal Gyrus and Insula. We assessed whether the integrator role of the STS within the temporal module also implicates a gatekeeper function (i.e., exclusively directing temporal module output to higher-order regions such as the IFG and insula; Supplementary Fig. 4). To this end, we compared the evidence for models with exclusive BM-specific modulation of effective connectivity between the STS and IFG/insula with evidence for models where effective connections linking the IFG and insula with MTC, FFG and/or STS were also modulated. Bayesian model reduction clearly indicated the optimal model was equipped with BM-specific modulation of all connections between the MTC, FFG, STS on one hand, and the IFG and insula on the other (model 1; family-wise posterior probability 100 %). These results do not speak in favour of a gatekeeper role of the STS but rather underline significant contributions of the FFG and MTC processing to the network, as they exhibit BM-specific projections to higher regions in parallel to the STS.

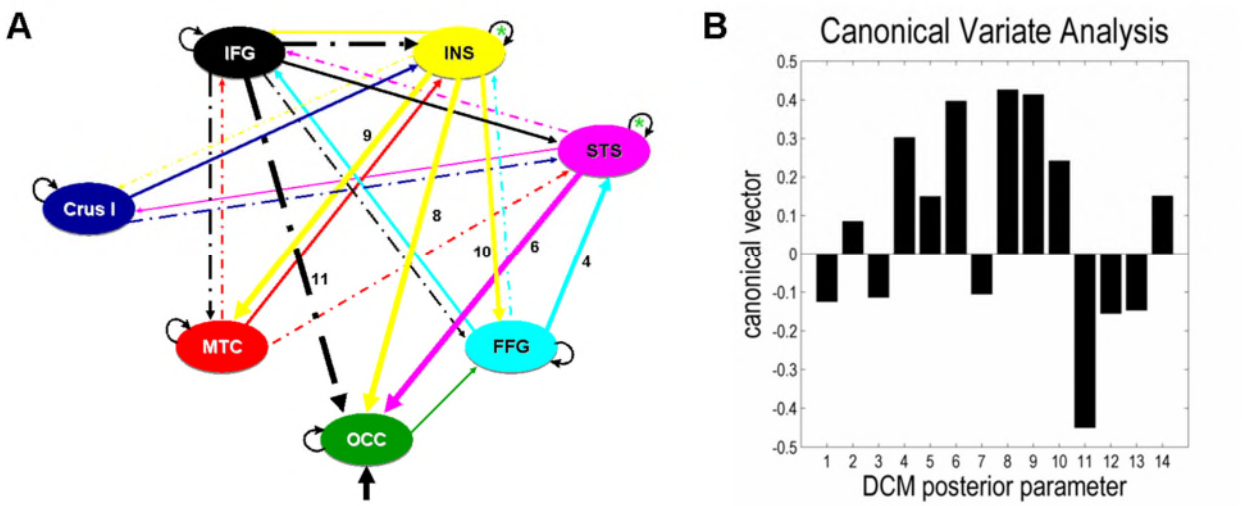

Fig. 2. Modulation of effective connections during the processing of BM – and relationship between BM-specific changes in connectivity and visual sensitivity to BM. (*A*) Bayesian model averaging of changes in effective connectivity during visual processing of BM over the entire network. These results provided very strong evidence (posterior probability of a particular BM effect being present at or above 95 %) that (i) effective connectivity from the MTC to the STS and from the FFG to the STS, but not between FFG and MTC was modulated by processing of BM; (ii) reciprocal connections between MTC/FFG and IFG/insula as well as between STS and IFG, but not between STS and insula were modulated by BM processing; (iii) insula outputs were predominantly enhanced by BM, whereas BM processing exerted an inhibitory effect on IFG outputs. Both regions also exhibited BM-specific crosstalk. Furthermore, BM modulated the connection from the early visual cortex (OCC) to FFG (but not from OCC to MTC), from the STS to OCC, and bidirectional connectivity between left lateral cerebellar lobule Crus I with the insula and STS (in different ways). Self-connections of the insula and STS (green asterisks) were also modulated by BM. Solid lines represent excitatory and dashed lines inhibitory effects, with arrow thickness corresponding to connection strength. Black numbers label the connections with the largest canonical vectors in the (*B*) mapping of the relationship between BM-specific changes in effective connectivity and visual sensitivity to BM ($p = 0.03$). These between-subject effects were afforded by a canonical variate analysis: Individual levels of BM modulation of top-down connections from IFG to OCC (parameter 11), insula to OCC (8), insula to MTC (9) and STS to OCC (6) served as best predictors of individual visual sensitivity to BM (as measured by d-prime). Modulations of the connections from the FFG to STS (4) and from the insula to FFG (10) also played important roles. Only modulatory parameters within the model space spanned by our three hypotheses and with posterior probabilities at or above 95 % at the group level were included in the canonical variate analysis.

Modulation of Top-Down Influences by Biological Motion Processing. Bayesian model reduction yielded a family-wise posterior probability of 100% for models in which BM modulates top-down connections from the IFG, insula and STS to the early visual cortex (OCC; Supplementary Fig. 5). Bayesian model averaging indicated divergent profiles of modulation: BM processing has excitatory effects on connections from the insula to OCC, MTC and FFG, and on the connection from the STS to OCC; but inhibitory effects on connections from the

IFG to OCC, MTC and FFG (Fig. 2*A*). Overall, this outcome suggests that the early visual cortex receives BM-specific top-down influences, and may indicate differential contributions of the STS, insula and IFG to the BM processing network.

Effective Connectivity Predicts Behaviour. The relationship between BM-specific changes in effective connectivity and visual sensitivity to BM was assessed at the between-subject level using a canonical variate analysis. This analysis included modulatory parameters that reached a posterior probability of 95 % in Bayesian model averaging over the entire network. Canonical variate analysis revealed a significant mapping between BM modulatory parameters and d-prime, measuring visual sensitivity to BM ($p = 0.03$; Fig. 2*B*). The principle canonical vectors suggested that visual sensitivity was best predicted by top-down effects from the IFG to OCC, the insula to OCC, and the insula to MTC and STS to OCC (in descending order). Other strong predictors of visual sensitivity to BM were the modulatory parameters on the connections from the FFG to STS and from the insula to FFG.

Structural Pathway between FFG and STS and Its Relationship to BM Detection. The group structural adjacency matrix derived from probabilistic tractography indicated white-matter connectivity between the FFG and STS (Supplementary Fig. 2*A*). At a single subject level, significant structural connectivity (at 5 % of the robust intensity range corresponding to a 95 % confidence interval; 45) were found in five out of 12 participants (Fig. 3*A*). Participants with significant FFG-STS structural connectivity exhibited higher BM hit rates than subjects without significant connectivity (Mann-Whitney test $U = 0$; $p = 0.003$; two-tailed, effect size $r = 0.8$). In contrast, d-prime, a measure of visual sensitivity to BM (that accounts for both hit and false alarm rates) did not significantly differ between the two groups ($U = 11$; $p > 0.05$). This pathway therefore appears to play a specific role in detecting BM, but not in discrimination between noise and camouflaged BM.

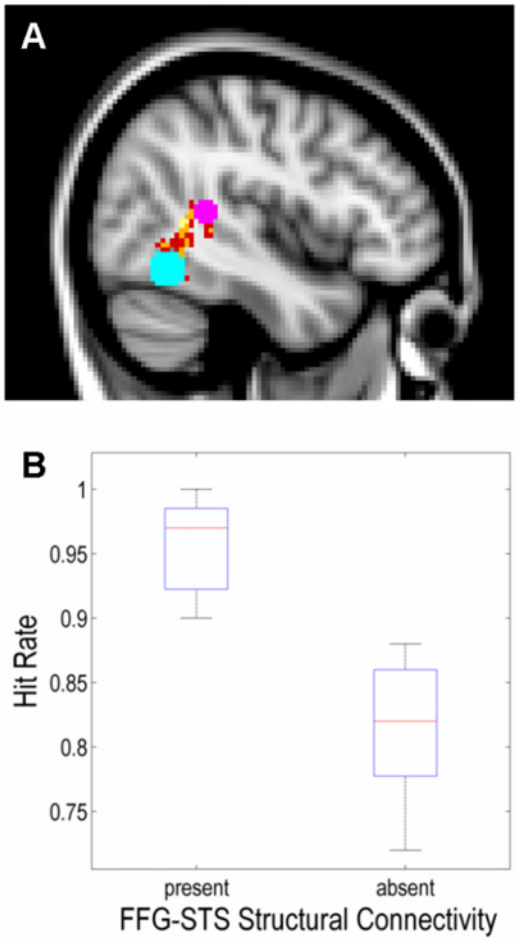

Fig. 3. White-matter pathway between the FFG and STS, and relationship between prevalence of significant FFG-STS structural connectivity and detection of camouflaged BM. (*A*) The group variability map over probabilistic tractography output in five participants with significant pathways (at a threshold of 5 % of the robust intensity range, corresponding to a confidence interval of 95 %) between the STS (purple) and FFG (cyan) illustrates the trajectory of connecting fibres. (*B*) Subjects with significant structural connectivity between the FFG and STS (left boxplot) have a higher BM detection (hit) rate as compared to subjects with non-significant FFG-STS connectivity (right boxplot; Mann-Whitney U = 0; p = 0.003). The median value of each group is represented by the red line. The top and bottom edges of the box indicate the 75th and 25th percentiles, respectively. The whiskers correspond to the highest and lowest hit rates in each group.

Discussion

The integrative analysis of structural and effective connectivity and their relationship to behaviour unveils several principles of functional integration within the network engaged in processing of BM. The outcome confirms that the right STS plays an integrative role within the temporal module. However, involvement of ventral and medial temporal cortices in the BM network appears to go beyond mere ‘pre-processing’ for the STS. Furthermore, the right STS,

insula and IFG exert substantial BM-specific top-down influences on the early visual cortex. The visual sensitivity to BM is best predicted by specific modulations of these top-down effective connections, as well as structural and effective connectivity between the FFG and STS.

The Temporal BM Processing Module: All Roads Lead… to the STS?

The right posterior STS is considered a cornerstone of the BM network (9-15, 17-19, 46-52). Consequently, the right STS has been put forward as an integrator within and between social brain networks (3). A recent analysis of functional connectivity during various social perception tasks including BM processing supported this view (28). The present DCM analysis confirmed an integrative role of the STS in the temporal module, by indicating specific modulation of the effective connections from the FFG and MTC to STS during BM processing.

The STS Is *Not* a Gatekeeper of the Temporal Module

Bayesian model comparison revealed BM-specific modulation of effective connectivity between MTC and FFG on one hand and the IFG and insula on the other. The data thus indicate BM-specific contributions from the FFG and MTC to the entire network and do not support a gatekeeper function of the STS within the temporal module. Whereas previous research reported activation in the FFG and MTC during BM processing (11, 16, 20-22, 27), their contribution to the network underwriting BM remained largely unclear. Patient studies in relatively small groups with heterogeneous occipito-temporal lesions yielded controversial results concerning the eloquence of these brain areas for BM processing (53, 54). One may speculate their engagement during visual perception of camouflaged BM provides the network with form-related information (55, 56), with the extrastriate body area in the MTC believed to be rather involved in processing of body parts, and the FFG in global body representation (57, 58).

Pathway between the FFG and STS is Crucial for BM Detection

Significant associations between behaviour, effective and structural connectivity point to a particular role of the pathway from the FFG to STS in BM processing. Previous research reported higher BOLD activation in both the STS and FFG accompanied by improvements in visual sensitivity to camouflaged BM after training (16). Conclusions on effective (40, 59, 60) and structural connectivity (61-64) between the FFG and STS were mainly derived from research on face processing and remained controversial, in particular with respect to detection of a structural pathway. The present findings indicated one-way effective connectivity from the FFG to STS with the strength of BM-specific modulation on this connection serving as a key predictor for the visual sensitivity to camouflaged BM.

Most important, corresponding structural connectivity was seen in about half of the participants. Given the orientation of the pathway perpendicular to the predominant fibre direction in this region (Fig. 3*A*), these insights may be attributable to the improved signal-to-noise ratio of the present HARDI dataset, related to the number of gradient directions and b-value (65, 66). Moreover, the finding of a higher BM detection rate in participants with measurable FFG-STS fibre pathways may underline previously assumed neurobiological between-subject variability (62, 63). Altered connectivity between the FFG and STS has been shown to contribute to deficient social perception in individuals with ASD (67). The present outcome therefore calls for further investigation of this connection's functional contribution to social cognition.

Top-down Modulation of Early Visual Cortex Matters

Strikingly, BM does not only modulate top-down connections from the IFG, insula and STS to the ventral and medial temporal cortex, but also to the early visual cortex. Furthermore, the strengths of these modulations are among the strongest predictors of visual sensitivity to BM (Fig. 3*B*). Previous psychophysical work suggested processing of camouflaged BM may depend on predictions (e.g., characteristic motion patterns) stored in higher hierarchical processing

levels (68, 69). The divergent effects of projections from the IFG (inhibitory), the STS and insula (excitatory) suggest these nodes may shape network activity and BM processing in different ways.

Under a predictive coding scheme (70), prediction errors in the early visual cortex (i.e., the discrepancy between predicted and sensed visual input) could be minimized by outputs from the IFG driving the activity of inhibitory interneurons (71, 72). Conversely, reliability of sensory information may be enhanced by attentional mechanisms reducing the gain of inhibitory interneurons (73) through feedback from the STS and insula. Such top-down modulation of the early visual cortex is considered indispensable for selective attention (74) and, according to high-resolution 7T fMRI, mainly reaches superficial layers almost exclusively populated by inhibitory interneurons (75). The present findings may indicate a more specific role of the early visual cortex in the network for BM processing than previously assumed. Illustrating the recruitment of such ipsi- and contralateral top-down projections to occipito-temporal areas may contribute to further conceptualizing non-conscious BM processing in individuals with damage to the early visual cortex (76, 77).

The Lateral Cerebellum Interacts with the Insula

The BM-specific top-down modulation by the right anterior insula may be related to its putative role as interface of internal and external body awareness (78), also reflected in implication of the insula in self-motion awareness (79), imitation (80), the sense of agency (81), anosognosia for hemiparesis (82) and out-of-body illusions (83). Interestingly, the present study indicates the left lateral cerebellar lobule Crus I also entertains effective connectivity loops with the insula (albeit without evidence for underlying direct structural connectivity), and not only with the STS as previously shown (26). In keeping with an overarching functional hypothesis for the cerebellum (84), the higher-level BM-specific predictions may be fine-tuned by the cerebellum, potentially having subsequent modulatory effects on the entire network via the cortical regions' distributed projections.

Network Approaches Bear Clinical Implications

Clinical evidence for the eloquence of single brain regions in BM perception is sparse, apart from the parieto-occipital white matter (85), the IFG and areas adjacent to the parieto-temporal junction (24) and the left lateral cerebellum (86). This relative lack of consistent findings may be due to methodological challenges such as heterogeneity of focal lesions and sample size, but may also indicate parallel instead of strictly hierarchical processing of BM. Parallel processing, as demonstrated in the present study, would be consistent with reports of altered visual sensitivity to BM in neuropsychiatric conditions such as autism (87-89) or schizophrenia (90-92), which are associated with more distributed network alterations (93, 94). Indeed, the local efficiency of intrinsic functional networks derived from resting-state fMRI data is related to behavioural variability in BM perception in healthy participants (95).

In autistic children, fMRI activation for intact as compared to scrambled BM in the social brain (including the STS, FFG, amygdala and insula) predicts the efficacy of social communication interventions (96). The social significance of BM is further underlined by reduced visual preference to BM in newborns with high familial risk of autism as opposed to those with a low risk (97). Inclusion of neuroimaging in studies of patients with focal lesions and neuropsychiatric conditions (98, 99) along with integrative network-level analyses such as implemented in this study may afford a better understanding of altered social cognition and could also inform clinical care.

Moreover, the methodological approach and data presented here may further promote investigation of the networks for body language reading, as well as their variability (3, 5, 100, 101). Among other factors, gender, presence of neuropsychiatric conditions and the body language content itself may affect the decoding of intentions or emotions from dynamic point-light and full-light bodily stimuli (102-108). Previous data implicate the STS and IFG in emotion and personality judgements based on point-light BM (109, 110). In both typically developing and autistic adults, a positive correlation was found between emotion recognition

accuracy from point-light BM and activity within the right STS (111). In male observers, same-gender full-light BM expressing threat selectively increases activation in a neural circuitry rather similar to the one reported here (103). Yet, the conceptualisation of the networks involved in body language reading remains largely incomplete. Integrative analyses of structural and effective connectivity and their association to behaviour may bridge this gap and potentially shed light on interactions between the cerebro-cerebellar circuitry for BM processing and limbic structures.

Conclusions

In summary, the present integrative analysis of structural and effective connectivity suggests the network for BM processing is organised in a parallel rather than strictly hierarchical manner. This organisation of the BM network appears neurobiologically plausible, and aligns with recent experimental evidence and conceptual considerations challenging the traditional view of a strictly hierarchical organization of visual processing (112-114). The data highlight the significance of top-down modulations by the insula, STS and IFG as well as the pathway from the FFG to the STS for veridical processing of BM. This work may inform future patient studies addressing the relationship between network pathology, deficient BM processing and associated impairment in social cognition.

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Materials and Methods

Participants and Experimental Procedures. 15 right-handed, typically developing male subjects (age 26.0 ± 1.04 years) were studied, with normal visual acuity and without history of neurological or psychiatric conditions or treatment. The group of participants overlapped with that in previous studies on non-camouflaged BM (26, 115). The fMRI and HARDI data have been used for a methodological illustration of the structurally informed parametric empirical Bayes (si-PEB) analysis of structural and effective connectivity (41) implemented in the present study. Two subjects had to be discarded from data analysis because of technical problems in stimulus presentation, and another because of a failure to follow instructions. Recruitment of participants of the same gender and handedness ensured a homogenous group, and thus avoided potential confounds. Handedness has been reported to influence lateralisation of static face and body processing (116). Haemodynamic response in females fluctuates with menstrual cycle (117), and both haemodynamic and neuromagnetic brain responses to BM appear to be sex-specific (118, 119). The study was approved by the Ethics Committee of the University of Tübingen Medical School, Germany. Subjects provided informed written consent and received financial compensation for study participation.

The camouflaged point-light BM displays (Supplementary Fig. 1) were inspired by a previous neuroimaging study (18). In brief, the stimuli consisted of a human walker represented by 11 bright dots on the head and main joints of the body, facing to the right and moving without net translation, with a walking speed of about 48 cycles per minute and each walking cycle lasting 62 frames (frame duration 20 ms). The point-light walker was simultaneously masked by 33 additional bright moving dots, created by random spatial distribution of three sets of the 11 dots comprising the original walker configuration on the screen, thereby preserving motion characteristics, size and luminance of the dots. The other stimulus type was a walker-absent display matching the spatial density of the walker-present stimuli, consisting of four scrambled walker sets (in total, 44 dots). Cutting's algorithm (120) was used to create the stimuli and the software Presentation (Neurobehavioral Systems Inc., Albany, CA, USA) to display them. The stimuli were projected onto a screen outside the MRI scanner to be seen by the participants

through a tilted mirror installed on the head coil, subtending a visual angle of about 12° vertically and 18° horizontally. Each stimulus was presented for 1000 ms, interleaved with a fixation cross (also during rest). In a two-alternative forced choice paradigm, the participants had to decide whether a walker was present or absent, pressing the respective button with their right index finger (button order counterbalanced between participants).

MRI Recording and Analysis. A 3T scanner (TimTrio, Siemens Medical Solutions, Erlangen, Germany; 12-channel head coil) was used for data acquisition. A three-dimensional T1-weighted magnetisation-prepared rapid gradient echo (MPRAGE; 176 sagittal slices, TR = 2300 ms, TE = 2.92 ms, TI = 1100 ms, voxel size = 1×1×1 mm^3) dataset served as anatomical reference. After field-map acquisition, two echo-planar imaging sessions (EPI; 114 volumes, 56 axial slices, TR = 4000 ms, TE = 35 ms, in-plane resolution 2 x 2 mm^2, slice thickness = 2 mm, 1 mm gap) were performed while participants were engaged with the BM task. Stimulus onset intervals were jittered between 4000 and 8000 ms in steps of 500 ms and stimulus order was pseudo-randomised, in order to improve estimation of the event-related response function. In total, 120 stimuli were presented during EPI recording (60 trials per condition), resulting in a session duration of 456 s each – containing an initial baseline epoch of 24 s, followed by three event-related epochs of 120 s interleaved with three baseline epochs of 24 s. HARDI data (54 axial slices, TR = 7800 ms, TE = 108 ms, slice thickness = 2.5 mm, matrix size = 88 × 88, field of view = 216 mm; 64 diffusion gradient directions; b-value = 2600 s/mm^2; one volume without diffusion sensitisation (b-value = 0 s/mm^2) per session) were acquired over two sessions, in order to improve consistency and sensitivity of diffusion parameter estimation.

Structural and fMRI data were pre-processed and normalised with standard procedures using Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (MathWorks, Inc., Sherbon, MA, USA). The pre-processed fMRI data were concatenated over both recording sessions and a general linear model (GLM) was used for statistical analysis of regionally specific effects.

A single regressor modelled stimulus onsets over the concatenated sessions. The stimulus type was represented by a parametric regressor (positive for stimuli containing a point-light walker; negative for stimuli without walker). In order to account for physiological artefacts, six head motion parameters, white-matter and cerebrospinal fluid time series were included as regressors of no interest. The event-related regressors were then convolved with a haemodynamic response function. Data were high-pass filtered (cut-off frequency of 1/256 Hz) and serial autocorrelations were accounted for by an error term modelled as a first-order autoregressive process with a coefficient of 0.2 mixed with white noise. Subsequently, for the contrasts task (positive first regressor) and walker-present trials (positive parametric regressor), individual whole-brain parameter contrast maps were created and submitted to second-level random effects analyses in the usual way. The resulting statistical parametric maps were thresholded at $p < 0.05$ (family-wise error whole-brain corrected for multiple comparisons using random field theory), and activation sites localised with automated anatomical labelling in SPM (121) and the NeuroSynth.org database (122; http://neurosynth.org).

The structural connectivity analysis on the HARDI data was conducted with the FMRIB's Diffusion Toolbox (FDT) within the FMRIB Software Library (FSL5, Oxford Centre for Functional MRI of the Brain, UK, http://www.fmrib.ox.ac.uk/fsl). As for the structural and functional MRI analysis, details are presented in detail elsewhere (41). In brief, Bayesian estimation of diffusion parameters obtained using sampling techniques with modelling of crossing fibres (BEDPOSTX; 65) on individual normalised HARDI data yielded voxel-wise diffusion parameters, used in subsequent probabilistic tractography with crossing fibers (PROBTRACKX; 65; step length = 0.5 mm, number of steps = 2000, number of pathways = 5000, curvature threshold = 0.2, modified Euler integration) with every node of the network derived from the fMRI analysis introduced as a spherical image with the same coordinates and radius as for DCM (please see below). Every node was used as seed for tractography to other regions (targets). For every voxel in the seed, PROBTRACKX provided counts of streamlines connecting this voxel to a voxel in a specific target. Averaging these streamline counts per

target across all voxels in the seed afforded a measure of structural connectivity. The procedure was repeated for every specified combination of seeds and targets in every subject until the individual structural adjacency matrices were complete. Of note, due to absent evidence for anatomical connectivity, structural connectivity between the left lateral cerebellar lobule Crus I and early visual cortex and FFG was not assessed. The fiber pathways were visually inspected to ensure plausibility. As tractography may yield different results based on which node is used as seed and target, for each pair of nodes an average for the two-way streamline counts was calculated, resulting in a symmetric weighted structural adjacency matrix per subject, further averaged across all participants to create a second-level matrix. These second-level structural connection strengths were used to constrain second-level PEB estimation on the individual DCMs (Supplementary Fig. 2*B*). When assessing the relationship between structural connectivity between the FFG and STS and performance on the BM task, individual symmetric structural connection strengths as described above were submitted to the correlation analysis. For analysis of the fibre pathway trajectory, the individual tractography outputs were thresholded at 5 % of the robust intensity range (corresponding to a 95 % confidence interval) and the resulting pathways converted to individual binary maps that were averaged across subjects, yielding a group variability map (Fig. 3*A*; 45).

Dynamic Causal Modelling. The DCM nodes were identified based on the fMRI analysis of regionally specific effects. Given previous results on right-hemispheric predominance in BM processing (27, 123, 124) and crossed cerebro-cerebellar communication (26), the 5 right cortical regions and the left lateral cerebellar lobule Crus I exhibiting increased BOLD activation for walker-present as compared to walker-absent stimuli were included in the DCM. A region in the early visual cortex (OCC) showing increased activation during visual stimulation as compared to baseline but without differential activation to BM was also included to accommodate visual driving input and to assess whether and how early visual cortex is affected by top-down afferents during BM processing.

The group coordinates were used to identify corresponding individual activation maxima (at $p < 0.05$, uncorrected), present in every participant within a maximum deviation of

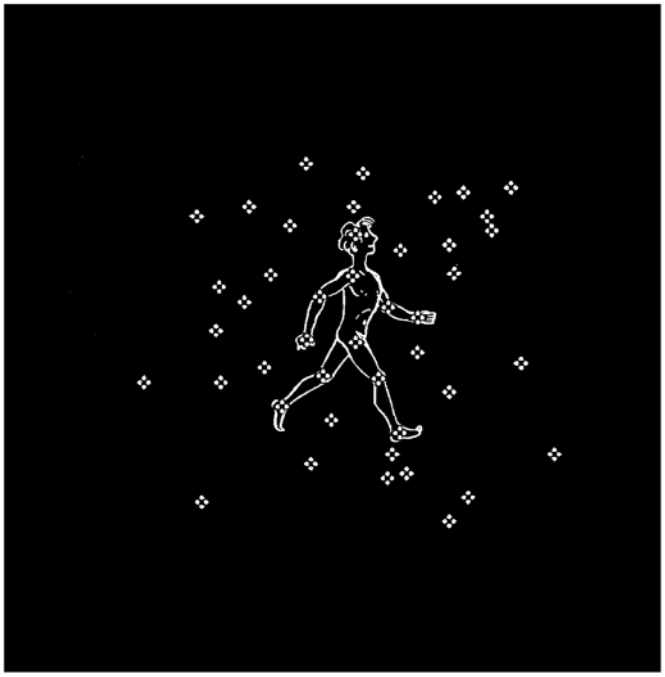
5 mm from the group activation coordinates. Corresponding time series were extracted by computing the first eigenvariate of all activated voxels within an 8 mm sphere centred on each individual maximum. Of note, the time series entering the DCM were pre-whitened as per standard SPM pre-processing procedures. This approach ensured the residuals of the DCM were approximately independent and identically distributed, fulfilling the normality assumptions of the model. Per subject, a one-state, bilinear and deterministic DCM with mean-centred inputs was specified, with reciprocal connections between all 7 nodes, except between OCC and the left cerebellar lobule Crus I, and FFG and the left cerebellar lobule Crus I (in accordance with the structural connectivity analysis). The parametric regressor (walker-present vs. walker-absent stimuli) was used to modulate all intrinsic (self-connections) and extrinsic (between-region) connections. Individual parameters and a second-level model of effective connectivity were estimated with the default SPM12 settings, including a Variational Bayes scheme under the Laplace approximation, yielding a multivariate normal density (43, 125). Integration of structural connectivity measures proceeded under the previously described si-PEB approach (41). Bayesian model reduction (43) provided the log-evidences of 405 models representing different mappings from structural connection strength to effective connection probability to determine the optimal constraints on effective connectivity. The second-level PEB and its effective connectivity parameters optimally constrained by structural connectivity were used for subsequent analyses and hypothesis testing.

Bayesian Model Comparison. We used BMR to assess our hypotheses on specific effects of BM processing on effective connectivity in the network. To this end, we specified models with different modulating effects of BM processing on effective connectivity in the temporal module, consisting of the MTC, FFG and STS (factor 1; number of hypotheses n = 16); on effective connectivity between MTC, FFG and STS on one side and insula and IFG on the other (factor 2; n = 8); and on top-down connections from the STS, insula and IFG to OCC (factor 3; n = 8). The different hypotheses per factor are illustrated in *Supporting Information*. All possible combinations of these factors within the three hypothesis sets resulted in 1024 models. Bayesian model reduction was used to assess the evidence for each of these models.

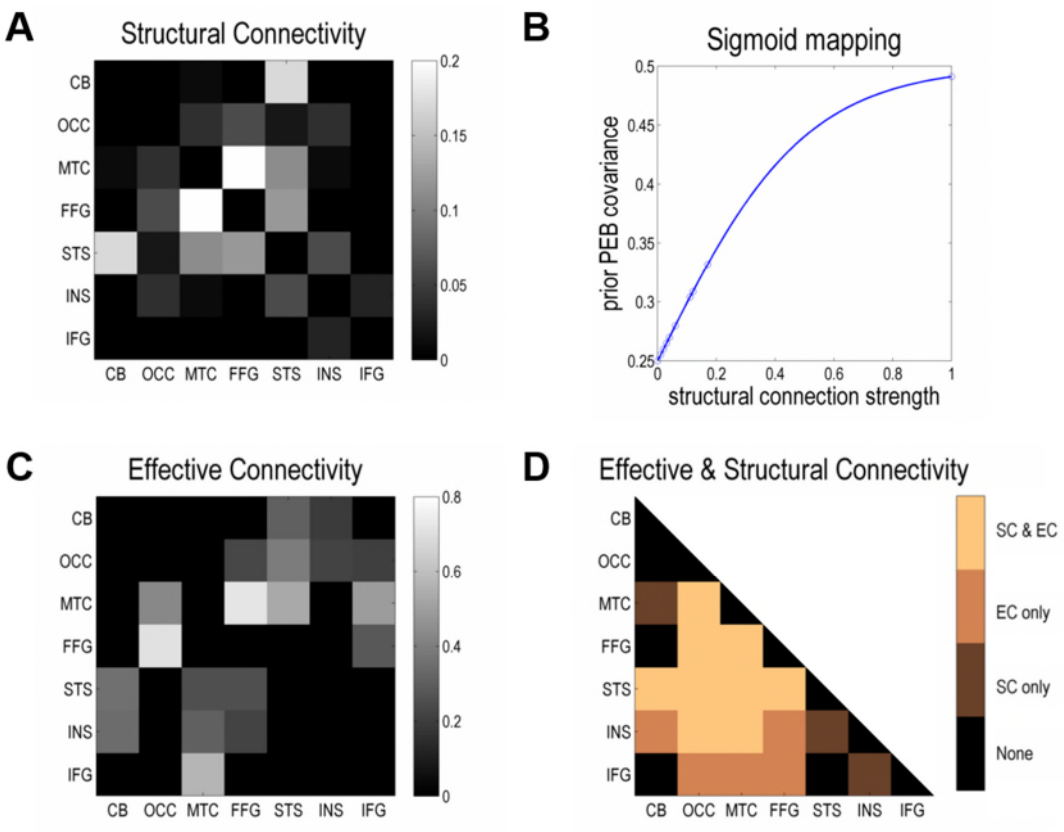
For each factor, log-evidences for models based on the same hypotheses were grouped in families and the evidence for the hypothesis assessed by a family-wise analysis (126). Finally, Bayesian model averaging across all 1024 models furnished the parameters encoding the modulating effects of BM, and their posterior probability.

Psychophysical and Canonical Variate Analysis. Visual sensitivity to BM was assessed with signal detection theory (42). The participants' replies to each trial were first classified as hits (correct detection of a walker), correct rejections (correct detection of a walker-absent trial), misses (no detection despite presence of walker), false alarms (indication of walker presence in its absence) or omissions (no response). The hit and false alarm rates per participant were calculated as the number of hits or false alarms compared to number of walker-present or walker-absent trials, respectively. These measures were used to calculate individual and group d-prime values; representing visual sensitivity to BM. For assessment of how connectivity relates to visual sensitivity, the participant-specific parameters of modulation by BM on connections within the space defined by our hypotheses (at or above a posterior probability of 95 %) were submitted to a canonical variate analysis with the corresponding d-prime values. Non-parametric Mann-Whitney U tests were used to determine whether individual d-prime values and hit rates differed significantly between subjects with and without significant structural connectivity between the FFG and STS.

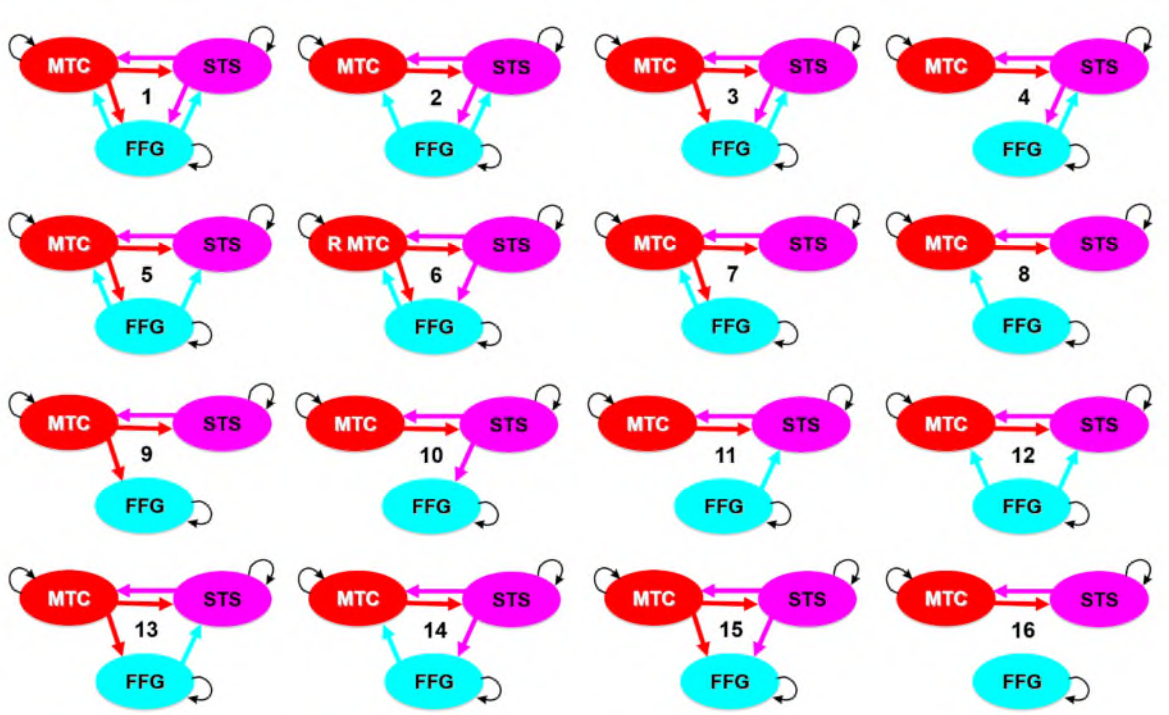
Supporting Information



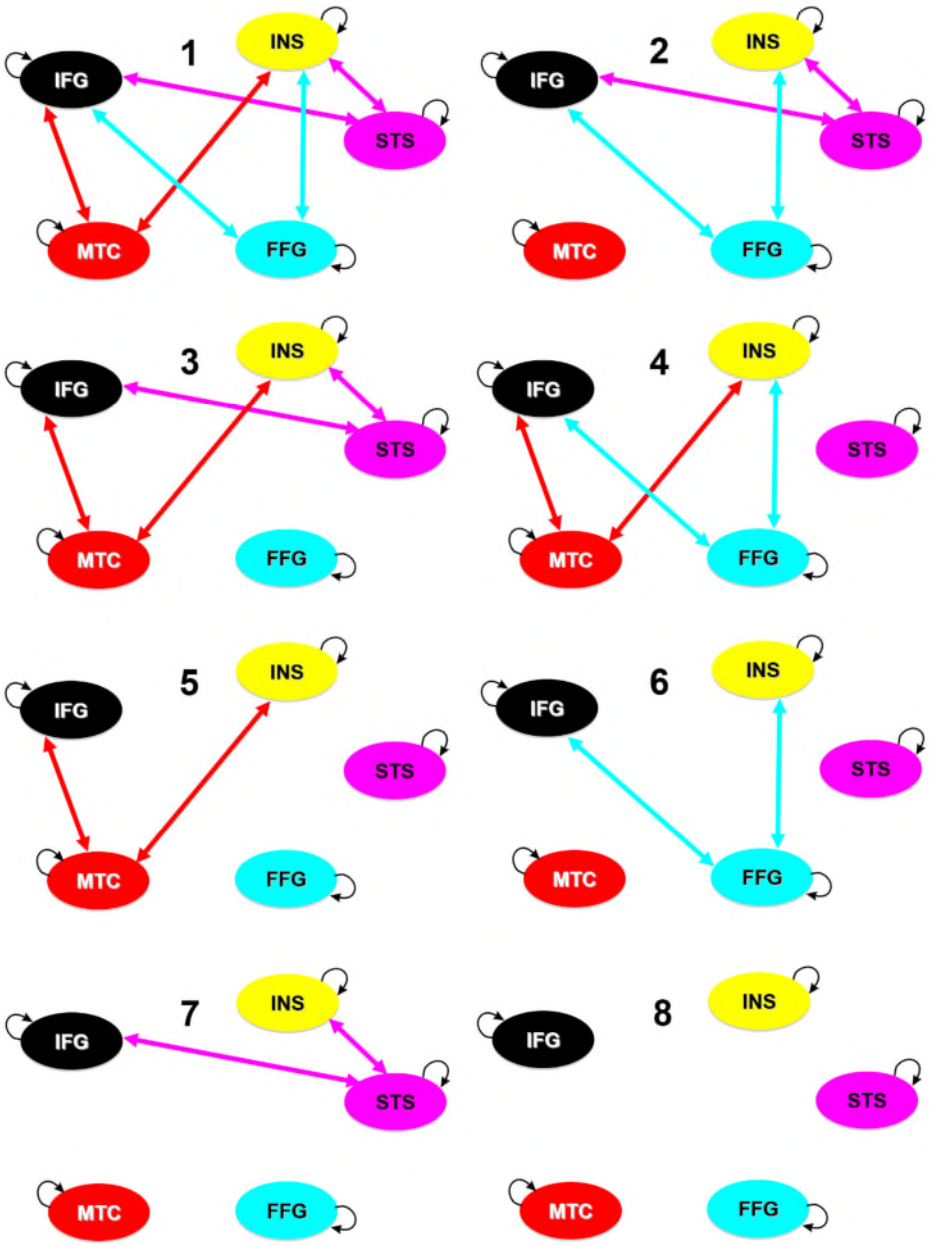
Supplementary Fig. 1. The camouflaged biological motion stimulus. Eleven bright dots placed on the head and major joints of a human body facing right and walking as if on a treadmill represented the point-light walking figure. An outline has been added for illustration purposes. 33 additional bright dots, each moving in the same way as one of the dots forming the point-light walker, were randomly distributed across the screen. Reprinted from (18), with permission from Elsevier.



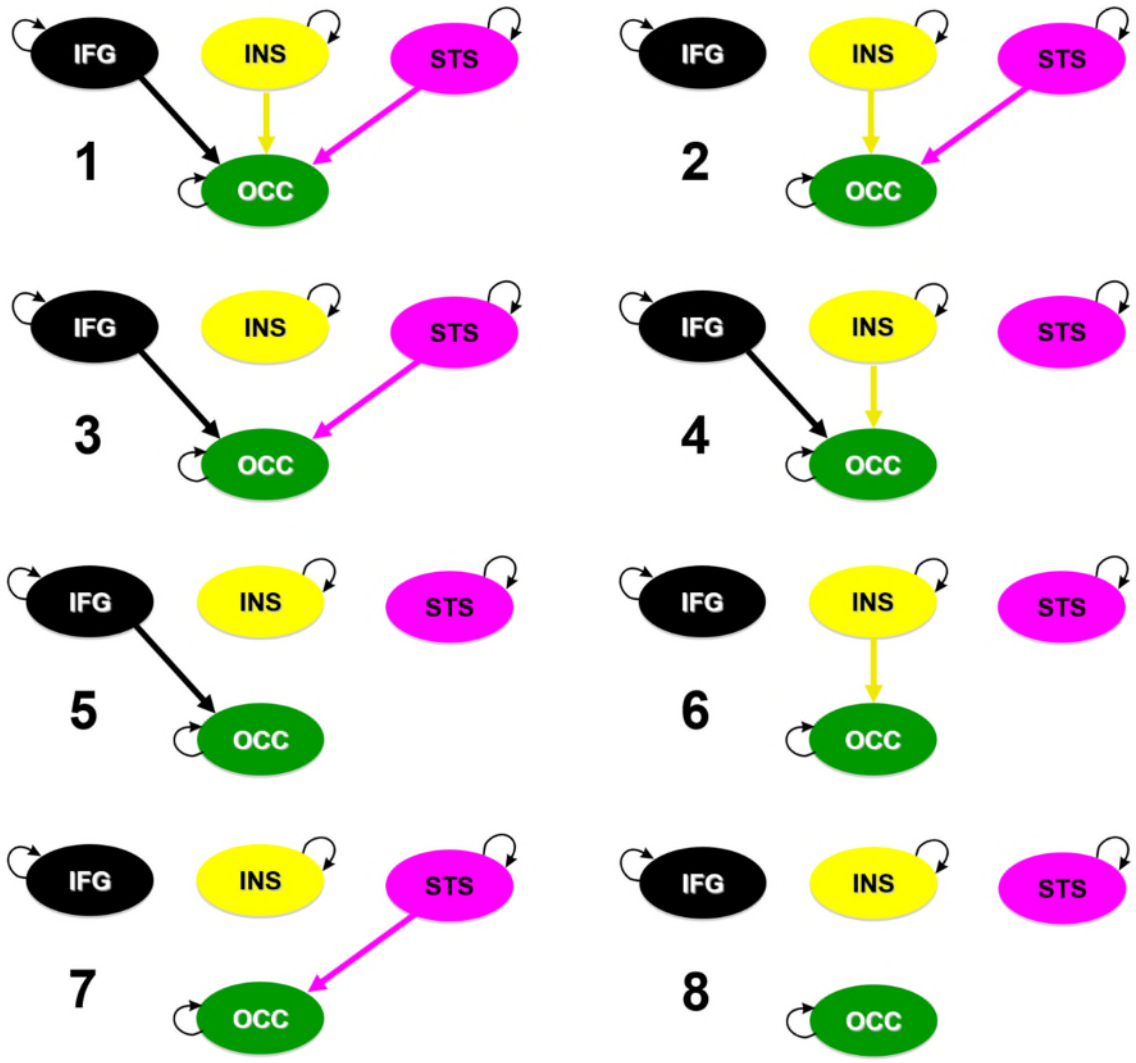
Supplementary Fig. 2. Effective and structural connectivity. (*A*) The symmetric structural connectivity matrix was scaled to the maximum connection strength (between FFG and MTC). Substantial connectivity was seen in the temporal module (MTC, FFG and STS). White-matter pathways also connect the insula with the MTC and early visual cortex, and the STS with the left lateral cerebellar lobule Crus I. (*B*) The mapping from structural connection strengths to the group-level prior probability of effective connectivity that afforded the optimal model of effective connectivity. This optimal mapping had hyperparameters $\alpha = 0$ (intercept of the sigmoid), $\delta = 4$ (slope of the sigmoid) and $\Sigma_{y\,max} = 0.5$ (maximum prior probability for effective connectivity). Blue circles represent how the single structural connection strengths relate to prior probability. (*C*) The parameters of between-region effective connectivity shown in this matrix were based on the optimal mapping between structural and effective connectivity. The columns represent directed output from the respective region. The effective connection from the FFG to MTC has the greatest strength, corresponding to the strongest structural connection, followed by effective connectivity from OCC to FFG. Parameters are provided in absolute values. (*D*) This adjacency matrix reports the convergence between structural and effective connectivity and indicates direct structural pathways accounted for nearly two thirds (9/14) of effective connections within this network; with a particular overlap in the right temporal module (connections between MTC, FFG and STS). Consequently, the five effective connections without underlying structural connectivity are polysynaptic, mediated via hidden nodes (regions not specified in the network model). No evidence for effective connectivity was found (at a posterior probability of 95 %) along three pathways afforded by probabilistic tractography. These results illustrate that structural connectivity can improve the evidence of models of effective connectivity. The convergence is shown with different colour codes (legend to the right of the map). A triangle was used to illustrate the matrix since structural connectivity is symmetric and, consequently, effective connectivity was considered present if the posterior probability was at 95 % or above for at least one of two possible connection parameters between two regions.



Supplementary Fig. 3. Modulation of the effective connectivity in the temporal module by BM processing. The 16 different hypotheses on how connectivity between the FFG and MTC, and between the FFG and STS is modulated during visual processing of camouflaged BM. In the full model (model 1), all effective connections in the temporal module are modulated by BM. Absent arrows in the other 15 models indicate an absence of modulatory effects of BM on the respective connection. The model space also included a null hypothesis where effective connectivity from or to the FFG is not modulated by BM.



Supplementary Fig. 4. Assessment of a "gatekeeper" function of the STS in the temporal module. In this model space, the evidence for models with different BM modulation patterns on reciprocal effective connectivity between the MTC and FFG on one side, and the IFG and insula on the other, as compared to exclusive BM modulation of the effective connections between STS and IFG/insula (model 7), that would correspond to a "gatekeeper" function of the STS.



Supplementary Fig. 5. Evaluation of BM-specific modulation of top-down effective connections from the IFG, insula and STS to the early visual cortex (OCC). Absent arrows in indicate an absence of modulatory effects of BM on the respective connection.

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