When gaze opens the channel for communication: Integrative role of IFG and MPFC

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ABSTRACT

Recent advances in the field of cognitive neuroscience have revealed that direct gaze modulates activity in cortical and subcortical key regions of the ‘social brain network’, including the inferior frontal gyrus (IFG) and the anterior rostral medial prefrontal cortex (arMPFC). However, very little is known about how direct gaze is processed during live interaction with a real partner. Here, for the first time we used an experimental setup allowing the participant inside an MRI scanner to interact face-to-face with a partner located in the scanner room. Depending on condition, the participant and the partner were instructed either to look at each other in the eyes or to direct their gaze away from the other. As control conditions, participants gazed at their own eyes, reflected in a mirror, or gazed at a picture of the partner’s eyes. Results revealed that direct gaze by the partner was associated with activity in areas involved in production and comprehension of language and action, including the IFG, the premotor cortex (PM), and the supplementary motor area (SMA). Activations in these areas were observed regardless of the participant’s gaze behavior. In contrast, increased activity in arMPFC, an area involved in inference of other mental states during social interaction and communication, was only observed when the participant reciprocated the partner’s direct gaze so as to establish mutual gaze. Psychophysiological interaction (PPI) analysis revealed effective connectivity between the IFG and the arMPFC during mutual gaze. This suggests that, within a larger network concerned with the processing of social gaze, mutual gaze with a real partner is established by an increased coupling between areas involved in the detection of communicative intentions, language, and social interaction.

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Introduction

Successful communication between two people depends first on the recognition of the intention to communicate. There are many ways by which this intention can be conveyed. A subtle yet effective way to initiate a conversation without actually speaking is to look directly at the other person (Cary, 1978). From infancy, humans are extremely sensitive to direct gaze and appreciate its significance in the initiation of communicative acts (Senju and Johnson, 2009; Senju et al., 2008). For example, it has been demonstrated that 6-month-old infants only follow the adult’s gaze towards an object—a potential communicative referential signal—when such an act is preceded by ostensive cues like infant-directed speech or direct gaze (Senju et al., 2008).

In adults, neuroimaging evidence suggests that direct gaze modulates activity in several cortical and subcortical key regions of the ‘social brain network’ (Frith, 2007), including the superior temporal sulcus (STS), the anterior rostral medial prefrontal cortex (arMPFC), and the amygdala (Senju and Johnson, 2009). Yet, the precise neural mechanisms underlying the processing of direct gaze during real interaction, remain unexplored to date. Indeed, until recently, social cognition has been mainly studied from a detached, observational perspective in tasks involving inert social stimuli (Becchio et al., 2010; Hari and Kujala, 2009; Schilbach et al., 2013). In line with this tradition, early fMRI studies seeking to ascertain the neural basis of the effect of direct gaze adopted simplified paradigms in which static displays of faces and eyes or brief video clips were presented to passive observers (for
a review, see Frischen et al., 2007). In recent years, more interactive paradigms have been developed by combining eye-tracking and virtual reality technologies (e.g., Schilbach et al., 2010; Wilms et al., 2010) and using live video feeds (e.g., Redcay et al., 2010; Saito et al., 2010; for a review, see Babiloni and Astolfi, 2014; Pfeiffer et al., 2013). These paradigms allow participants not only to react to the other's gaze, but also to observe an agent moving its eyes in a gaze contingent fashion—that is, in response to the participant's own gaze behavior. Despite their usefulness in characterizing gaze-contingent responses, however, they do not allow true face-to-face interaction and may thus lack 'the potential for real social interaction' (Skarratt et al., 2012).

In the context of a 'live' encounter, the other's gaze is not something that can be subsumed into a strictly visual representation of eye direction: it has an impact on the observer's own system that sets the observer up for further response (Gallagher, 2014). Accordingly, perception of the other's gaze presents not just a perceptual pattern. It involves complex interactive behavioral and neural response patterns and affords a 'unique type of interaction' (Gangopadhyay and Schilbach, 2012), which may remain beyond the reach of paradigms manipulating gaze contingency within virtual and video setups.

To capture this specific aspect of gaze-based interaction arising out of active engagement with a 'live' person, here we used an experimental setup allowing the participant inside an MRI scanner to interact face-to-face with a real partner. The partner—a co-experimenter—stood in the scanner room, close to the machine, behind the participant, within his/her social space (Hall, 1966). His face was visible to the participant through a 45° oriented mirror located inside the scanner in front of participant's eyes. Depending on condition, the participant and the co-experimenter were instructed to look at each other in the eyes (so to reciprocate the partner's direct gaze and establish mutual gaze) or to turn their gaze away (so to avoid the partner's direct gaze). As controls, participants had to gaze at a picture of the partner's eyes or at their own eyes as reflected in a mirror. In both these situations, participants saw a face with a direct gaze without encountering any true interaction with another person.

Consistent with the proposal that being looked at by live person elicits a response from the observer (Gallagher, 2014), we expected that, in comparison to both averted gaze and control conditions, direct gaze by the co-experimenter would activate regions critical for preparing a communicative response. These areas include the inferior frontal gyrus (IFG), the premotor cortex (PM), the left anterior insula (AI), and the supplementary motor area (SMA; Alario et al., 2006; Brendel et al., 2010; Riecker et al., 2005). The IFG, in particular, has been consistently implicated in both comprehension and production of language and action (Fadiga et al., 2009; Fazio et al., 2009). Its role in social gaze, however, is less clear as only some of the studies examining direct gaze have shown increased activity in this region (Kuzmanovic et al., 2009; Pelphrey et al., 2004; Pierno et al., 2006, 2008; Saito et al., 2010; Tanabe et al., 2012). A recent proposal (Pfeiffer et al., 2013) relates IFG to the establishment of a communicative intent and suggests that IFG activity may open the 'channel for social interaction' (Cary, 1978), providing some kind of 'readiness potential' for initiating a gaze-based interaction (see also, Saito et al., 2010).

With this in mind, we hypothesized a functional association between IFG and mentalizing areas implicated in social interaction and communication (Amadio and Frith, 2006; Frith and Frith, 2006, 2010) during mutual gaze. More specifically, we expected that during mutual gaze, recruitment of the IFG would increase in coupling with that of the arMPFC, a key region of the 'social brain network', consistently activated across a wide range of mentalizing tasks (Amadio and Frith, 2006) and proposed to play a prominent role in modulating the processing of visual information in social contexts (Schilbach et al., 2013). To test this hypothesis, in addition to the conventional univariate analysis, we conducted psychophysiological interaction (PPI, Friston et al., 1997) analysis using IFG as seed region.

**Materials and methods**

**Participants**

Twenty one right-handed volunteers (9 women and 12 men; average age: 23) were recruited at the University of Minnesota. None of them had a history of neurological, major medical, or psychiatric disorders. Before the study participants gave their written informed consent. Specific information about the study was provided after the experimental session. Experimental procedures and scanning protocols were approved by the Institutional Review Board and conducted in accordance with the principles of the revised Helsinki Declaration (World Medical Association General Assembly, 2008). None of the individuals taking part in the experiment experienced any discomfort during fMRI acquisition.

**Procedure and design**

During the entire experiment, the participant (P) laid in supine position in the bore of the MRI scanner, while an experimenter (E), who was the same person for all the experimental sessions (male, aged 54), sat in the scanning room. The distance between P's head and E's head was about 150 cm and was constant throughout the study. A large mirror was positioned in the back of the scanner's bore at a distance of approximately 50 cm from the scanner. P viewed the large mirror via a tilted mirror attached to the top of the head coil at a distance of 15 cm from P's eyes. When the large mirror was positioned obliquely (at 45°), P could see E's gaze reflected in the head coil mirror, with a clear view of E's gaze direction. A white carton board, held up by E, ensured that only the upper part of E's face (from the nasal bone to the forehead) was visible to P. When the large mirror was positioned orthogonally (at 90°), E could see P's gaze reflected in the head coil mirror, with a clear view of E's gaze direction. A white carton board, held up by E, ensured that only the upper part of E's face (from the nasal bone to the forehead) was visible to P. When the large mirror was positioned obliquely (at 45°), P could see E's own gaze (from the nasal bone to the forehead) reflected in the head coil mirror. The distance between the eyes of P and those of E was the same as twice the distance between the eyes of P and the large mirror. This ensured that for the participant the image of his/her own eyes had the same size as the image of E's eyes.

The experiment consisted of five different conditions, each one described by the gaze behavior of P and E. In the (Look, Look) condition, P and E were instructed to establish mutual gaze by looking at each other directly in the eyes. In the (Look, Not Look) condition, P looked at E, whose gaze was oriented 30° left away from P. In the (Not Look, Look) condition the opposite took place: at the beginning of the trial, P was instructed to direct his/her gaze 30° away from E and look at the magnet bore, while E looked straight at P. Despite the gaze behavior of E being the same as in the (Look, Look) condition, P's view was therefore completely different. Based on instructions, P knew that E was looking at him/her, but he/she could not discriminate E's gaze direction. In the (Look Picture) condition, P was asked to look at a still picture displaying E's face and eyes looking straight ahead. The pictured pasted on a white carton board, was held up by E at the eye level, thus covering his real face. Finally, in the (Look Yourself) condition, the participant was asked to look at his/her own eyes reflected in the mirror. In all five conditions, the gaze direction was constantly monitored by another co-experimenter via a camera to guarantee the correct execution of the task. Each participant was randomly assigned to one of two possible experimental sessions. In the first session, each condition, lasting 30 s, was presented four times. In the second session, each condition was presented six times and lasted 15 s. In both sessions, a 20 second break, in which participants were asked to keep their eyes closed, was included after each condition. Within each session, trials were presented in pseudo-random order (maximum of two trials of the same condition in a row).

**MRI data acquisition**

The experiment was carried out on a whole body 3 Tesla scanner (Magneton Trio, Siemens Medical Center, Erlangen, Germany) equipped with a standard Siemens 32-channel coil. Functional images were
acquired with a gradient-echo, echo-planar (EPI) T2*-weighted sequence in order to measure blood oxygenation level-dependent (BOLD) contrast throughout the whole brain (30 slices acquired with ascending interleaved sequence, 1 mm gap between slices, 3.5 x 3.5 x 4.0 mm resolution, FOV = 192 x 192 mm, flip angle = 86°, TE = 35 ms). Volumes were acquired continuously with a repetition time (TR) of 2500 ms; depending on the experimental session, either 408 (first session) or 426 volumes (second session) were collected for each participant. Before the fMRI acquisition, 144 or 160 (depending on the participant’s head size) FLASH images were acquired (data matrix 256 x 256, 1 mm isotropic voxels, TR = 20 ms, TE = 4.7 ms).

MRI data analysis

Imaging data were analyzed using Brain Voyager QX (Brain Innovation, Maastricht, Holland). Functional data of each participant were preprocessed as follows. 3D motion correction was applied to adjust for small head movements. All volumes were spatially aligned to the first volume by rigid body transformations, using a trilinear interpolation algorithm. To cope with slice scanning time differences, slice scan time correction was applied using a cubic spline interpolation algorithm. Drifts due to scanner and physiological noise were removed using high-pass temporal filters acting on frequencies lower than 3 cycles in time course. After preprocessing, each participant’s slice-based functional scans were coregistered with their 3D high-resolution structural scan. 3D structural data for each participant were then transformed into Talairach space (Talairach and Tournoux, 1988). The cerebrum was rotated and translated into the AC-PC (AC = anterior commissure, PC = posterior commissure) plane and the borders of the cerebrum were identified. Using the anatomical–functional coregistration matrix and manually determined Talairach reference points, the functional time course of each participant was then transformed into Talairach space and the volume time course was created using a Gaussian full width at half maximum (FWHM) kernel of 7 mm. For each participant, a protocol file (PRT) was then derived representing the onset and duration of the events for the five conditions and rest periods: i) Look, Look; ii) Look, Not Look; iii) No Look, Look; iv) Picture; v) Look Yourself; vi) Break. In order to account for hemodynamic delay and dispersion, each of the predictors of interest (i.e. 5 conditions) was derived by convolution of an appropriate box-car waveform with a double-gamma hemodynamic response function to extract brain regions with both positively and negatively correlated blood oxygen level dependent (BOLD) responses. These predictors were entered as fixed factors in single subject GLM; then, the parameter estimates of this GLM model were subsequently entered into a second level of analysis corresponding to a random-effect GLM model that was used for group analysis (Penny and Holmes, 2003). The statistical parameters of this latter model were estimated voxelwise for the entire brain and activation maps were computed for various contrasts between the predictors. To formally identify regions that were activated by the direct gaze of E regardless of P’s gaze direction, a (Look, Look) ∩ (Not Look, Look)]) conjunction analysis was applied. The resulting activated clusters were determined using the automated routines in Brain Voyager. For all the statistical comparisons, correction for multiple tests was performed using the false discovery rate (FDR; Genovese et al., 2002), with a q value of 0.05.

Psychophysiological interaction analysis

PPI enables determination of brain regions whose activity shows a change in correlation with a seed region (the “physiological” component of the PPI) as a function of a change in the participants’ psychological state (the “psychological” component of the PPI; e.g., Spunt and Lieberman, 2012). Here, a PPI analysis was conducted to examine how IFG (BA 44), used as seed region, coupled with other brain regions as a function of P’s gaze behavior (Look, Look vs Not Look, Look). To this end, for each participant we extracted the time course of activity in the IFG with a 6 mm radial sphere using the voxel showing peak activity for the contrast (Look, Look vs Not Look; x = −41 y = 17 z = 10). We then z-transformed the time course values and we generated the PPI regressor by multiplying the physiological regressor (time course of IFG) by the convolved psychological regressor (the difference between Look, Look−Not Look, Look conditions). For each participant, both the physiological and the PPI regressors were added to the original design matrix. The resulting matrices were finally entered into a random-effects group analysis in which the PPI regressor was tested. Correction for multiple tests was performed using the false discovery rate (FDR; Genovese et al., 2002), with a q value of 0.05.

Results

The random effects ANOVA with ‘Condition’ as within subjects factor revealed differential bilateral activations in the IFG (BA 44), the anterior insula (AI, BA 13), the premotor cortex (PM, BA 6), the middle frontal gyrus (medial frontal eye field, FEF, BA 6), the anterior and posterior intraparietal sulci (aIPS and pIPS, BA 7), the fusiform gyrus (FG, BA 19), the inferior occipital gyrus (IOG, BA 18), the parahippocampal gyrus (pAHG, BA 36), along with the thalamus, the ventral striatum, and the globus pallidus. Differential activity was also observed in the arMPFC (BA 9), the anterior cingulate (ACC, BA 24), the left supplementary motor area (SMA, BA 6), and the right superior temporal sulcus (pSTS, BA 22).

The peak of activity and stereotaxic coordinates for activations resulting from contrasts of interest are listed in Table 1. All other contrasts are listed in Supplementary Table 1. Contrasting the (Look, Look) condition with the (Look, Not Look) condition revealed a bilateral increase in neural activity in the IFG (BA 44/45), the AI (BA 13), and the PM (BA 6). Additional foci of activation for this contrast were observed in the left SMA (BA 6), the arMPFC (BA 9), and the ACC (BA 24). As can be seen in Table 1, this pattern of activation shares many similarities with that associated with the (Look, Look vs. Look Picture) and the (Look, Look vs. Look Yourself) contrasts (Fig. 1). In particular, two foci in the IFG (BA 44/45) and in the AI (BA 13) were observed bilaterally in all contrasts. An overlap in the activation patterns revealed by the contrasts (Look, Look vs. Look, Not Look), (Look, Look vs. Look Picture), and (Look, Look vs. Look Yourself) was also observed in the left SMA (BA 6), in the arMPFC (BA 9), and in the ACC (BA 24). Outside these regions, the contrasts (Look, Look vs. Look Picture) and (Look, Look vs. Look Yourself) also yielded differential activity within the right pSTS (BA 22).

Contrasting the (Look, Look) condition with the (Not Look, Look) condition revealed differential activation in the arMPFC (BA 9). Inspection of the effect sizes, confirmed that, at variance with activity in the IFG, the AI, and the SMA, activity in this region was specifically driven by reciprocation of direct gaze (see Fig. 2). A bilateral increase of activity was also found in the FG (BA 19) and the IOG (BA 18). The inverse contrast (Not Look, Look vs. Look, Look) revealed a bilateral enhanced activity in the pIPS, the aIPS (BA 7), and the medial FEF (BA 6).

To examine the regions that were active in response to direct gaze by E regardless of P’s gaze direction a conjunction analysis of the (Look, Look) and (Not Look, Look) conditions was performed. The analysis revealed a bilateral response in the IFG (BA 44/45), the AI (BA 13), the SMA (BA 6), the primary visual cortex (V1, BA 19), the IOG (BA 18), the FG (BA 19), and the right thalamus along with the putamen, the claustrum and the medial and lateral globus pallidus, bilaterally.

Finally, PPI analysis was conducted to identify areas more functionally connected during the (Look, Look) condition in comparison to the (Not Look, Look) condition. PPI revealed effective connectivity between the left IFG, used as seed region, the arMPFC (BA 9; Talairach coordinates: x = −2 y = 55 z = 14) and the left AI (BA, 13; x = −40 y = −9 z = 3). Additional increased coupling of the left IFG was shown in left middle temporal gyrus (MTG, BA 21), left inferior parietal lobe (IPL, BA 40), left PM (BA 6), right putamen, bilateral superior temporal gyrus (STG, BA 41) bilateral ACC (BA 24) and bilateral claustrum.
Discussion

In interactive contexts, the other’s gaze is irreducible to a visual representation of eye direction. Direct gaze by the other signals a communicative intent and demands a response (Gallagher, 2014). To capture this specific aspect, here we used an experimental setup allowing the participant inside an MRI scanner to interact in real time and face-to-face with a partner located outside the scanner.

When the gaze of others opens the channel for communication

Within an action-oriented account of social perception, perception of intentionality has been proposed to trigger a unique sort of action
planning, resulting in the recruitment of brain regions involved in action monitoring, response inhibition, motor preparatory processes, and communicative intentions (Gangopadhyay and Schilbach, 2012). In accordance with this hypothesis, differences in physiological as well as subjective evaluative responses have been reported to seeing the picture of a person on a computer monitor vs. seeing a person ‘live’ through a liquid crystal shutter (Hietanen et al., 2008; Pönkänen et al., 2008, 2011a,b).

Here, we found that in comparison to averted gaze, direct gaze by a live partner engaged the IFG, the AI, and the SMA. A highly similar pattern of activation was revealed when direct gaze by the partner was contrasted with conditions in which participants saw a pair of eyes without encountering any true interaction with another person, i.e., with the picture of a face displaying direct gaze (Look Picture) or with the participant’s own gaze reflected in a mirror (Look Yourself). This suggests that these substrates do not encode the mere visual input of two eyes directed to the observer, but are specifically related to the demand of a responsive action in the other’s direct gaze.

IFG has been implicated in language production and comprehension as well as in several non-language-related cognitive functions (Fadiga et al., 2009; Fadiga and Craighero, 2006), including action execution and observation (as a crucial node of the mirror-neuron system; Becchio et al., 2012; Clerget et al., 2009; Fazio et al., 2009; Heiser et al., 2003; Iacoboni et al., 1999). Together with left SMA, to which it is directly connected (Vergani et al., 2014), it has been ascribed a specific function in the initiation of speech (Eickhoff et al., 2009). In a related way, the SMA plays a crucial role not only in the execution of action sequences, but also in their preparation and initiation. For example, it has been shown that reversible inactivation of SMA in monkeys affects the initiation of self-paced action sequences (Kermadi et al., 1997). Some authors have thus associated SMA with the development of the intention to act (Goldberg, 1985). Moreover, as proven by both fMRI and neuropsychological data, the SMA is crucial for speech initiation, operating as a ‘starting mechanism’ of speech production (Brendel et al., 2010). Patients with lesions to the left SMA may often exhibit diminished spontaneous verbal utterances, accompanied by a lack of spontaneous initiation of speech (Fontaine et al., 2002; Masdeu et al., 1978; Pai, 1999; Rostomily et al., 1991), resulting in the so-called transcortical motor aphasia (Masdeu et al., 1978).

In the context of the present study, we suggest that IFG and SMA activity may be specifically related to the establishment of a communicative intent (Buccino et al., 2004) and the preparation of a communicative response (Pfeiffer et al., 2013). This is further supported by the conjunction of the (Look, Look) and (Not Look, Look) conditions. At first sight, no common property seems available in the visual input of the two conditions. However, when the level of representation is raised to the level of mental states (Teufel et al., 2010), these conditions are both characterized by the experience of being watched—and thus implicitly addressed—by another person. This is in line with recent findings showing that the observer’s knowledge of being the target of another individual’s attention has a major role in governing the reactions to another person’s eye gaze: even when the other person’s eyes are not visible, the mere belief of being seen is sufficient to enhance autonomic and cortical responses to direct gaze (Myllyneva and Hietanen, 2015).

In concordance with the hypothesis that direct gaze by a real partner exerts an affective impact on the observer (Gallagher, 2014), the results further demonstrated differential effects for direct gaze as compared to averted gaze in the ACC and the ventral striatum. These regions have been consistently activated in studies of social reward, including playing a game with an alleged human partner, experiencing pleasant touch (Walter et al., 2005), and viewing an attractive face displaying direct gaze (Kampe et al., 2001). Redcay et al. (2010) recently found that the ACC and the ventral striatum are engaged to a greater extent during contingent interaction via live video feed than during viewing of the
same stimuli via recorded video. Along similar lines, Schilbach et al. (2010) reported increased striatal activation during self-initiated joint attention in comparison to other-initiated joint attention. The finding that a real face displaying direct gaze but not a picture of a face displaying direct gaze or the participant’s own gaze reflected in a mirror engages the ACC and the ventral striatum adds to this notion, suggesting that reward activation are not associated to direct gaze per se, but relate to the initiation of social interactions. This might provide a neural mechanism for the pervasive drive for humans to seek out social interactions (see also Redcay et al., 2010; Schilbach et al., 2010) and might indeed explain why interaction with a real partner is experienced as intrinsically rewarding (Tomasello, 2009).

Mutual gaze closes the loop between minds

To assess the impact of the participant’s own gaze direction, depending on condition, participants were instructed to gaze at the partner (so to reciprocate the partner’s direct gaze and establish mutual gaze; Look, Look), or to turn their gaze away (so to avoid the partner’s direct gaze; No look, Look). Contrasting these conditions revealed that at variance with activity in the IFG, the PM and the SMA, activity in the aMPFC was specifically driven by reciprocation of direct gaze.

Located between the orbital and the posterior rostral region of the MFC, the aMPFC is involved across a wide range of social-cognitive tasks requiring the inference of mental states (Van Overwalle and Baetens, 2009). Intrusive gestures in different modalities (e.g., eye contact and calling your name, without a message following these signals) elicit activity in aMPFC (Kampe et al., 2003). Moreover, there is evidence that the aMPFC is more active when participants infer other individuals’ communicative intentions (e.g., to offer a book to another person) than when they reason about individual intentions (e.g., to look at the book; Ciaramidaro et al., 2014; Walter et al., 2004). This has led to the proposal that the aMPFC is involved in the special kind of representations that ‘close the loop between minds’, enabling communication about a shared world (Frith, 2007; Frith and Frith, 2010).

Mutual gaze has been described as “the most powerful mode of establishing a communicative link between humans” (Farroni et al., 2002). That aMPFC was selectively recruited during mutual gaze confirms and extends this interpretation, suggesting that this area may provide a neural substrate for the ‘meeting of minds’ regardless of the communicative channel—words, movements, or simply gaze—used to attain it. As indicated by PPI analysis, the recruitment of aMPFC during mutual gaze increased in coupling with the IFG seed. This finding speaks to the integrative role of IFG and aMPFC in social gaze processing and suggests that, during face-to-face interaction with a real partner, mutual gaze is established by an increased coupling between areas concerned with detecting and handling communicative intentions.

Interestingly, when participants were instructed to avoid the partner’s gaze (Not Look, Look vs. Look, Look), a pattern of activation consistent with that typically obtained in antisaccade tasks was observed (Ettinger et al., 2008). The bilateral activation of the posterior and anterior intraparietal sulcus (pIPS and aIPS, respectively), along with the activation of the medial FEF, are compatible with a model of conflict between a prepotent response (i.e., a reflexive saccade to the partner’s gaze), which must be inhibited, and a volitional response (i.e., an antisaccade), which must be generated instead (Munoz and Everling, 2004; Hutton and Everling, 2006). Not Look, Look, Look, Look,

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.06.025.

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