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Atypical activation of the mirror neuron system during perception of hand motion in autism

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ABSTRACT

Disorders in the autism spectrum are characterized by deficits in social and communication skills such as imitation, pragmatic language, theory of mind, and empathy. The discovery of the "mirror neuron system" (MNS) in macaque monkeys may provide a basis from which to explain some of the behavioral dysfunctions seen in individuals with autism spectrum disorders (ASD).We studied seven right-handed high-functioning male autistic and eight normal subjects (TD group) using functional magnetic resonance imaging during observation and execution of hand movements compared to a control condition (rest). The between group comparison of the contrast [observation versus rest] provided evidence of a bilateral greater activation of inferior frontal gyrus during observation of human motion than during rest for the ASD group than for the TD group. This hyperactivation of the pars opercularis (belonging to the MNS) during observation of human motion in autistic subjects provides strong support for the hypothesis of atypical activity of the MNS that may be at the core of the social deficits in autism.

1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder affecting as many as 1 in 165 children (Fombonne, 2003) or even in 90 children (King and Bearman, 2009) that is four times more prevalent in boys than in girls. ASD is usually diagnosed between the ages of 2 and 3 years, but early signs may be detectable by 12 months of age (Osterling and Dawson, 1994). As initially described by Kanner (1943), individuals with autism have three core features: impairments in reciprocal social interactions; abnormal development and use of language; and repetitive and ritualized behaviors and a narrow range of interests (American Psychiatric Association, 2000). ASD affects a variety of anatomical structures, from the cerebral cortex to the cerebellum and brainstem (Minshew and Williams, 2007). Impaired imitative skills in infancy may also reflect a functional dysfunction that accounts for autistic syndromes. For instance, Williams et al. (2001) suggested that imitation may be affected by a dysfunction of the mirror neuron system (MNS), producing the constellation of symptoms that characterize ASD.

Initially observed in the macaque monkey, mirror neurons discharge both when a monkey performs a motor act and when at rest it observes another individual (a human being or another monkey) performing a similar act. Mirror neurons

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were originally discovered in the ventral premotor cortex (monkey area F5) and have also been described in the PFG (prefrontal gyrus) and anterior intraparietal areas of the inferior parietal lobule (IPL, see Rizzolatti et al., 2009 for a review). There is now increasing evidence that the MNS has a role in understanding the actions of others. It has also been proposed that the MNS is part of a system underlying the imitation of actions (see Fabbri-Destro and Rizzolatti (2008) for a review).

In humans, the existence of an analogous system in the homologous brain region has been supported by non-invasive electrophysiological (e.g. EEG, MEG) and brain imaging (e.g. PET, functional MRI) and TMS (Fabbri-Destro and Rizzolatti, 2008).

For instance, studies using EEG have shown activation of the motor cerebral cortex, preferentially involving the left hemisphere and suppression of the mu (μ) rhythm, during observation of biological movement (Cochin et al., 1998; Muthukumaraswamy et al., 2004; Oberman et al., 2005). Moreover, a similar pattern of mu suppression, with the same activation during observation and execution of a movement has been shown in adults in the left hemisphere (at electrode site C3), which suggests that the same neuronal network is involved in the observation and the execution of a movement (Cochin et al., 1999). Observation of biological movement in normal children was found to be related to a significant decrease in theta 1 and theta 2 power values on EEG in the fronto-temporal and central regions of the left hemisphere compared with visual perception of motionless images or nonhuman movement (Cochin et al., 2001). It has even been shown in healthy children that human, animal and virtual movement activates different cortical areas (Martineau and Cochin, 2003). Oberman et al. (2005) used this phenomenon to test the mirror mechanism in children with high-functioning ASD. The results showed that, although individuals with ASD exhibited suppression of mu rhythm during voluntary movements, this suppression was absent when they watched someone else performing the same movement. Martineau et al. (2008) compared EEG activity during the observation of videos showing actions or still scenes in very young autistic children and control children (aged 5 years 3 months – 7 years 11 months) and showed desynchronisation of the EEG in the motor cerebral cortex and the frontal and temporal areas during observation of human actions in the group of healthy children. No such desynchronisation was found in autistic children. Moreover, inversion of the pattern of hemispheric activation was found in autistic children, with increased cortical activity in the right hemisphere in the posterior region, including the centro-parietal and temporo-occipital sites. Oberman et al. (2008) recently reported that mu suppression was sensitive to degree of familiarity. Both typically developing participants and those with ASD showed greater suppression in response to familiar hands compared to those of strangers. These findings suggest that the MNS in individuals with ASD responds to observed actions, but only when individuals can identify with the stimuli in a personal way. The recent study of Raymaekers et al. (2009) performed with high-functioning children between 8 and 13 years compared to typically developing peers did not support the hypothesis that ASD is associated with a dysfunctional MNS. Both groups show significant suppression of mu rhythm to self and observed hand movements. The differences observed between these studies can be partially due to the heterogeneity of the ASD population.

In an fMRI study performed to examine the mirror neuron system in ASD, high-functioning children with autism and matched controls were scanned (fMRI) while they imitated and observed emotional expressions (Dapretto et al., 2006). Markedly weaker activation was observed during the observation condition in the pars opercularis of the inferior frontal gyrus in children with ASD than in typically developing children. Interestingly, the degree of activation was inversely related to symptom severity.

The present study used a block paradigm fMRI design to investigate neural activity during the observation and execution of human movements in high-functioning young adults with autism. The aim of the study was to explore in autism the neural network involved in the observation and in the execution of biological movement.

2. Results

We first analyzed patterns of activation across situations within each group and then compared the results between the two groups.

2.1. *Execution > rest*

During the *execution of movement* versus *rest conditions*, activation in the typically developed (TD) group occurred in the left motor area. In the adult autism spectrum disorder group (ASD), we also observed clear activation in the left motor area and also in the right cerebellum. No difference was observed between the TD group and ASD group (Table 1).

2.2. *Observation > rest*

During the observation of movement versus rest conditions (Table 1), activation occurred in the TD group in the left intraparietal sulcus and bilateral occipital regions. In the ASD group, activation of the right motor area, bilateral inferior parietal lobule (supramarginalis gyrus) and bilateral occipital regions occurred. The between group comparison of observation versus rest conditions demonstrated greater activation of the bilateral inferior frontal gyrus (pars opercularis) during observation than during rest in the ASD group compared to the TD group (Fig. 1).

2.3. *Observation > execution*

Comparison between observation versus execution conditions in the TD group showed greater activation in the right lateral occipital regions and the right precuneus during observation compared to execution (Table 1). No difference between observation versus execution conditions was observed in the ASD group. No difference was observed between the ASD and TD groups for the observation versus execution comparison.

Table 1 – Brain activation for Execution versus Rest, Observation versus Rest, Observation versus Execution and Execution versus Observation. Results are shown for the Typically Developed group (TD), Autism Spectrum Disorders group (ASD) and for comparison between groups ($p<0.001$ non-corrected, cluster-wise correction with p value of cluster <0.05). MNI coordinates = Montreal Neurological Institute coordinates.

Execution > Rest	Side	MNI coordinates (mm)			*n* Voxels	Z-Score
		x	y	z		
TD group						
Central sulcus	L	−36	−28	70	521	4.81
ASD group						
Central sulcus	L	−32	−34	66	727	5.11
Central sulcus	L	−58	−22	48	78	3.99
Cerebellum (lobule 6/declive)	R	20	−42	−32	209	4.59
Observation > Rest	**Side**	**MNI Coordinates (mm)**			***n* Voxels**	**Z-Score**
		x	y	z		
TD group						
Parietal lobule (intraparietal sulcus)	L	−34	−50	54	171	4.55
Anterior occipital gyrus	L	−48	−70	−8	127	3.74
Anterior occipital gyrus	R	46	−68	2	429	4.44
ASD group						
Central sulcus	R	60	−18	42	136	4.5
Postcentral sulcus	R	30	−42	54	182	4.28
Parietal lobule (supramarginalis)	L	−50	−30	36	103	4.71
Parietal lobule (supramarginalis)	R	44	−26	22	62	4.62
Inferior occipital sulcus	L	−38	−74	−8	495	4.76
Inferior occipital sulcus	R	26	−90	14	159	4.57
Anterior occipital gyrus	L	−26	−84	24	59	3.74
Anterior occipital gyrus	R	38	−62	2	400	4.59
ASD group > TD group						
Inferior frontal gyrus (pars opercularis)	L	−56	20	20	161	4.70
Inferior frontal gyrus (pars opercularis)	R	52	12	12	142	4.42
Observation > Execution	**Side**	**MNI Coordinates (mm)**			***n* Voxels**	**Z-Score**
		x	y	z		
TD group						
Inferior occipital sulcus	R	42	−80	−4	100	5.02
Anterior occipital gyrus	R	36	−68	8	53	4.40
Anterior occipital gyrus	R	54	−60	0	50	4.08
Precuneus	L/R	4	−72	48	183	3.93
Superior occipital sulcus	R	28	−82	38	54	3.67
Execution > Observation	**Side**	**MNI Coordinates (mm)**			***n* Voxels**	**Z-Score**
		x	y	z		
ASD group						
Cerebellum (lobule 6/declive)	R	22	−44	−32	87	4.69
Central sulcus	L	−32	−26	52	35	3.71

2.4. *Execution > observation*

In the ASD group, the inverse comparison showed greater activation of the left central sulcus and right cerebellum for execution than for observation (Table 1). No difference between execution versus observation conditions was observed in the TD group, and no difference was observed between the ASD and TD groups for the execution versus observation comparison.

3. Discussion

In this study, active movement consisted of repetitive opening and closing of the hand. The pattern of brain activation (contralateral primary sensorimotor cortex) was the same in both groups. However, the ipsilateral cerebellum was activated only in ASD subjects, in accordance with Muller's study (Müller et al., 2004) showing increased motor activation

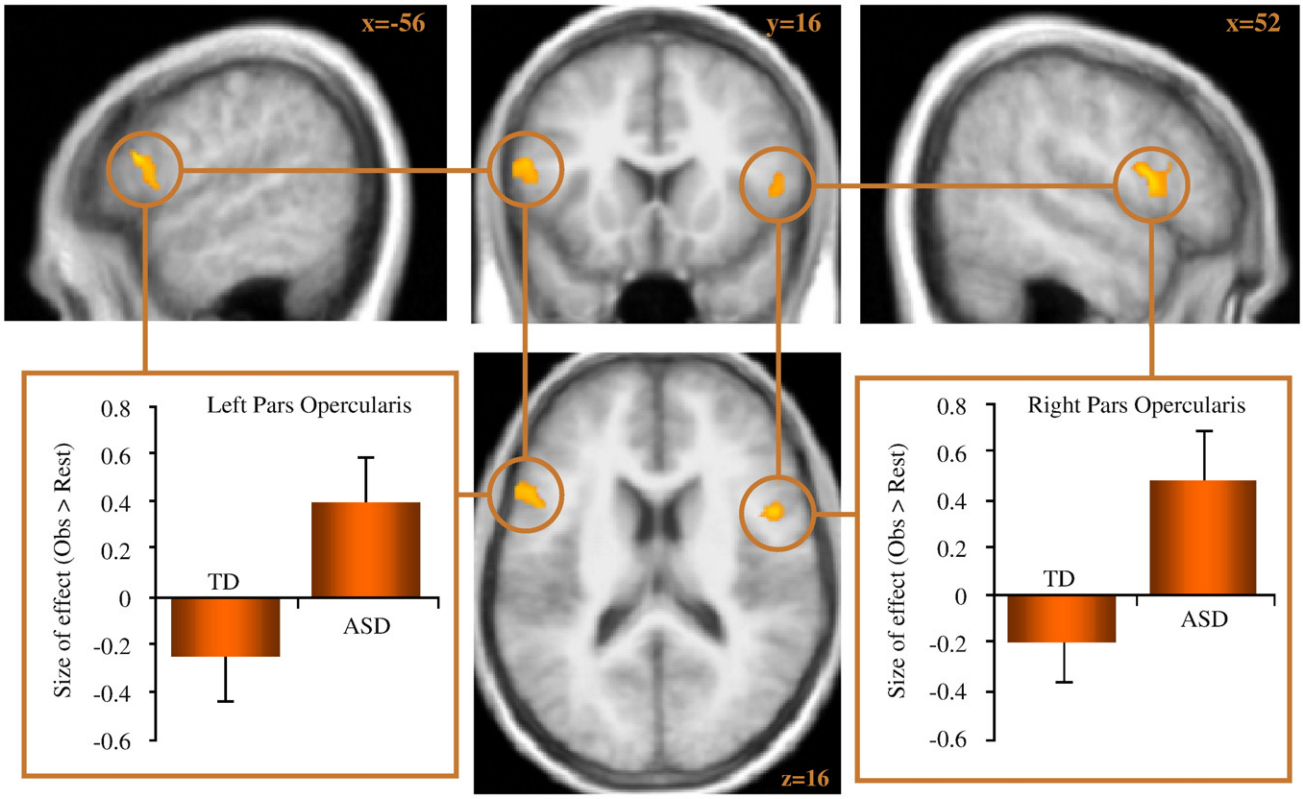

Fig. 1 – Between group comparison (ASD > TD) for observation versus rest contrasts. Results indicate that both left (x = −56 y = 20 z = 20; Z-score = 4.70) and right (x = 52 y = 12 z = 12; Z-score = 4.42) pars opercularis showed more activation in the ASD group than in the TD group ($p < 0.001$, non-corrected, cluster-wise correction with p value of cluster < 0.05). Size of effect was computed in both left and right cluster (bars = standard deviation) and showed that the pars opercularis was more highly activated for observation than for rest in the ASD group. Clusters are superimposed on the mean anatomical images of all subjects (8 TD subjects and 7 ASD subjects).

in the ipsilateral anterior cerebellar hemisphere in autistic subjects in a voluntary task compared to TD subjects. According to Müller et al. (2004), this finding strongly suggests dysfunction of the autistic cerebellum that reflects anatomic cerebellar abnormality. All MRI images have been examined by a neuroradiologist (JPC) and there was no evidence of cerebellar anatomic abnormality in ASD patients. The activation of the cerebellum in ASD during execution situation may simply mean that the task was difficult for them and requested more attention.

During the observation situation, left parietal (intraparietal sulcus) and inferior bilateral occipital regions were activated in TD subjects, and right central and post central, bilateral parietal (supramarginalis) and inferior bilateral occipital areas in ASD subjects. It is now established that humans possess a neural system called the mirror neuron system (MNS) that maps visual descriptions of actions performed by others onto the observer's motor representations of the same actions (Rizzolatti and Craighero (2004). In humans, the MNS has two major components; one is formed by the inferior parietal lobule, the ventral premotor cortex and part of Broca's area, and the other by the anterior cingulate gyrus and the insula (Rizzolatti and Craighero, 2004, Gallese et al., 2004). The areas of the intraparietal sulcus are situated between the higher parietal lobule (BA 5, more motor and somatosensorial) and the inferior parietal lobule (BA 7, more visual), the physiological responses of some of them being characterized like true interfaces between the sensory and motor cortices (Andersen et al., 1990). Apart from the sensorimotor aspects, the parietal cortex is also influenced by (even involved in) cognitive functions such as spatial attention (coding of attentional vectors, Goldberg et al., 1990; Colby and Duhamel, 1991, Cutrell and Marrocco, 2002; Colby and Goldberg, 1999 for a review) or intention to perform a movement (Duhamel et al., 1992; Colby and Duhamel, 1996). In particular, seven different areas can be distinguished in the intraparietal sulcus (IPS): three areas on its medial bank, V5, the MIP (medial intraparietal) and PIP (posterior intraparietal), in addition to part of the PO area (parieto-occipital); at least two areas in the bottom of the sulcus, the VIP (ventral intraparietal) and AIP (anterior intraparietal); and at least two areas on the lateral bank of the intraparietal sulcus, the LIPv and LIPd (lateral ventral and dorsal intraparietal). In our study, the IPS was activated in TD subjects and the supramarginalis in subjects with ASD. Those results demonstrate atypical activations of the parietal mirror neurons system in autism. The central and post central sulci were activated by observation of human movement only in autistic individuals but not in controls, demonstrating atypical

activation in autistic subjects. It is now recognized that the bilateral occipital areas are selective for visual processing of the human body (Downing et al., 2006) and these areas were activated in both groups.

The most striking result of this study was evidenced by the between groups comparison of observation versus rest contrast. This comparison revealed greater activation of the bilateral inferior frontal gyrus (pars opercularis) during observation of human motion than during rest for the ASD group compared to the TD group. Several researchers have undertaken studies to investigate the execution/observation matching system in individuals with autism (Avikainen et al., 1999; Hadjikhani et al., 2006; Oberman et al., 2005; Theoret et al., 2005, Williams et al., 2006, Bernier et al., 2007, Martineau et al., 2008). Differences between the ASD and TD groups have been found in activation of the MNS on fMRI (Dapretto et al., 2006, Williams et al., 2006). In contrast to our study, examining mirror neuron abnormalities in high-functioning children with autism, Dapretto et al. (2006) found no mirror neuron activity in the inferior frontal gyrus (pars opercularis) whereas they observed expression of emotions. Structural brain differences in mirror neuron regions have also been observed in adults (Hadjikhani et al., 2006). There is a possible explanation for our findings of hyperactivation of the pars opercularis in the ASD group during the observation of human motion compared to the TD group. The TD and ASD groups had different interpretations of the human action on the video screen. For the TD group, the observed action may have been too simple, without any biologically relevant information, whereas the action may have had relevant information for the ASD group. However, this hyperactivation of the pars opercularis in ASD subjects during the observation of human motion, evidenced by the intragroup comparison, provided strong support for the hypothesis of "atypical" activity of the MNS that may be at the core of the social disorders in autism.

Comparison between observation versus execution responses in controls evidenced mainly greater activation in the right precuneus during observation compared to execution. This cortical area has traditionally received little attention (see Cavanna and Trimble, 2006 for a review). Recent functional imaging findings in healthy subjects suggest a central role for the precuneus in a wide spectrum of highly integrated tasks, including visuo-spatial imagery (Wenderoth et al., 2005; Malouin et al., 2003; Suchan et al., 2002; Knauff et al., 2003), episodic memory retrieval (Lundstrom et al., 2005; Gilboa et al., 2004; Addis et al., 2004) and self-processing operations (Ruby and Decety, 2001, Vogeley et al., 2001; Den Ouden et al., 2005). The precuneus is amongst the brain structures displaying the highest resting metabolic rates (Gusnard and Raichle, 2001). It has therefore recently been proposed that the precuneus is involved in the interwoven network of the neural correlates of self-consciousness, engaged in self-related mental representations during rest (Kjaer and Lou, 2000). No difference between observation versus execution was observed for ASD individuals evidencing a dysfunction of precuneus activity. Measuring deactivation by means of rest-associated functional activity in the precuneus, Kennedy et al. (2006) found that the autism group failed to demonstrate this deactivation effect. The authors speculated that the lack of deactivation in the autism group was indicative of abnormal internally directed processes at rest, which may be a significant contribution to the social and emotional disorders of autism.

In summary, the AD group demonstrated typical activation when executing an action, suggesting intact sensorimotor systems underlying self-initiating actions, but demonstrated atypical activation during observation of human motion in various cerebral areas: i.e. the motor cortex, inferior frontal gyrus (pars opercularis), parietal lobule, and precuneus, suggesting faulty systems underlying the observation of biological movement. All these structures, among them the MNS, are involved in numerous functions and may contribute significantly to the social interaction and emotional disorders in autism. Atypical activation, either hypo- or hyperactivation of the circuitry that translates visual input into motor understanding can impact on social interaction. Further research to examine the relationships between activity in these areas and symptom severity are now needed to support the hypothesis that a dysfunctional "mirror neuron system" may underlie the social disorders observed in autism. The combination of fMRI and high resolution EEG recordings are also needed to clarify discrepancies between researches and elucidate the neural origin of ASD.

4. Experimental procedures

4.1. *Participants*

The participants comprised 7 high-functioning adult individuals with autism (all male, ASD group) between 19 and 31 years of age recruited through clinical departments and local agencies and 8 typically developed adult individuals (all male, TD group) recruited through local youth groups and matched for age and educational level to each autistic individual. IQ assessments were carried out using WAIS-IV. Because many ASD subjects prefer left hand use or even present a lack of clear handedness (Colby and Parkison, 1977; Cornish and Mc Manus, 1996), the handedness inventory was administered. All participants were right-handed (Edinburgh

Table 2 – Ages, Intelligence Quotients (VIQ = Verbal Intelligence Quotient, PIQ = Performance Intelligence Quotient, FSIQ = Full Scale Intelligence Quotient) and Handedness scores of ASD group (Edinburgh Handedness Inventory, laterality score given by R – L/R + L with R = number of actions realized by the right side and L = number of actions realized by the left side).

ASD group	Age (years)	VIQ	PIQ	FSIQ	Handness score
1	19	84	91	87	1
2	19	75	93	85	1
3	26	73	90	85	1
4	19	93	112	101	1
5	31	121	100	113	0.8
6	23	102	81	92	1
7	24	95	89	90	1

Table 3 – Ages and Handedness scores of TD group (Edinburgh Handedness Inventory, laterality score given by R–L/R+L with R = number of actions realized by the right side and L = number of actions realized by the left side).

TD group	Age (years)	Handness score
1	19	1
2	23	1
3	25	1
4	26	1
5	19	1
6	24	1
7	19	1
8	31	0.8

Handedness Inventory, laterality score up to 80). All participants were asked for details of any current psychotropic medication. Patients were excluded if they had a neurological disability, full scale IQ<70, or were not able to be exposed to MRI (e.g. possessing metal implants). Autistic participants had no identifiable etiology such as tuberous sclerosis or fragile-X syndrome. All participants were also required to be in good medical health, free of seizures and have no history of brain trauma. Permission for the study was granted by the local Medical Ethics Committee and all participants gave informed, signed consent. The ages of the ASD subjects are provided in Table 2, along with IQ scores (Verbal, performance and full scale IQ) and handedness scores, the ages and handedness scores of the TD subjects are provided in Table 3.

4.2. *MRI data acquisition*

Scanning was performed on a 1.5-T Signa General Electric scanner (GE, Milwaukee, WI, USA). Subjects lay supine in the scanner, their heads being secured with cushions in the head coil. One of the authors (JM) stayed near them to reassure them in case of need and to monitor the subject's behavior.

Structural images were acquired first, including a scout image to center the field of view on the subject's brain. Then 3 high resolution (0.93×0.93×1.5 mm) structural T1-weighted images (SPGR sequence; TR=21 ms; TE=6 ms) were acquired in the sagittal plane with different flip angles (25° for one series, 30° for the other two).

Subjects underwent two consecutive fMRI scans, each 4 min 30 s in length. In the two separate runs, subjects were instructed to either watch (observation condition) a videotape of a right hand performing a flexion–extension movement at a rate of 1 Hz, or execute (execution condition) the flexion–extension movement with their right hand at a rate of 1 Hz. During the control condition (rest) and the execution condition, they were requested to observe the static picture of the same hand. The videotape was presented to the subject using MR compatible goggles. Functional images were acquired using a single-shot planar echo imaging sequence sensitive to BOLD contrast (TR=3 s; TE=60 ms; flip angle=90°). The two blocked-task paradigm consisted of a functional run of 90 whole-brain acquisitions (25 contiguous slides, 5 mm thickness, 3.75×3.75 mm in-plane resolution, FOV=240 mm). The paradigm was explained to the subjects prior to scanning. Four 30 s blocks of active conditions (observation or execution) alternated with four 30 s blocks of rest.

4.3. *Imaging preprocessing*

Functional data were analyzed using the general linear model in SPM5 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm). All images were realigned, normalized to an EPI template (resampled voxel-size of 2×2×2 mm) and spatially smoothed (8 mm FWHM Gaussian kernel). A high-pass frequency filter (cutoff 120 s) and corrections for autocorrelation between scans were applied to the time series. Statistical analysis was performed using the general linear model implemented in SPM5, with a separate regressor for each block type ("Observation", "Execution", "Rest") convolved with a canonical haemodynamic response function.

4.4. *Imaging analysis*

Movement parameters from realignment corrections were entered as additional covariates of no interest to account for residual movement artifacts after realignment. Statistical parametric maps were generated from linear contrasts between the different situations for each participant. A second stage random-effect analysis was then performed using one-sample (TD group and patients with autism group) and two-sample (comparison between groups) *t*-tests on contrast images obtained in each subject for each comparison of interest. All contrasts were performed across the whole brain using standard threshold criteria (Worsley et al., 1996) of significant activation at a voxel-level of $p<.001$ (uncorrected) and a cluster-wise correction (p value of cluster <0.05). Average sizes of effect were extracted from all voxels in regions of interest, defined by the full-extent clusters showing significant activation at a voxel-level of $p<.001$ (uncorrected) in the SPM group analysis (random-effect contrasts).

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