

A meta-analysis of the anterior cingulate contribution to social pain

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Many functional magnetic resonance imaging studies have explored the neural correlates of social pain that results from social threat, exclusion, rejection, loss or negative evaluation. Although activations have consistently been reported within the anterior cingulate cortex (ACC), it remains unclear which ACC subdivision is particularly involved. To provide a quantitative estimation of the specific involvement of ACC subdivisions in social pain, we conducted a voxel-based meta-analysis. The literature search identified 46 articles that included 940 subjects, the majority of which used the cyberball task. Significant likelihoods of activation were found in both the ventral and dorsal ACC for both social pain elicitation and self-reported distress during social pain. Self-reported distress involved more specifically the subgenual and pregenual ACC than social pain-related contrasts. The cyberball task involved the anterior midcingulate cortex to a lesser extent than other experimental tasks. During social pain, children exhibited subgenual activations to a greater extent than adults. Finally, the ventro-dorsal gradient of ACC activations in cyberball studies was related to the length of exclusion phases. The present meta-analysis contributes to a better understanding of the role of ACC subdivisions in social pain, and it could be of particular importance for guiding future studies of social pain and its neural underpinnings.

Keywords: anterior cingulate cortex; cyberball; functional magnetic resonance imaging; meta-analysis; social pain

INTRODUCTION

Social connection and avoidance of painful experiences are considered basic needs of human beings (Baumeister and Leary, 1995). In recent years, many research teams have investigated the neural correlates of social interactions, especially social pain, which could be defined as 'the unpleasant experience that is associated with actual or potential damage to one's sense of social connection or social value owing to social rejection, exclusion, negative social evaluation or loss' (Eisenberger, 2012b). For identifying the neural correlates of social pain, several experimental paradigms were designed; however, the cyberball task is by far the most widely used paradigm. The cyberball task is held to be a gold standard paradigm for the study of social rejection (Williams *et al.*, 2000). During this task, participants are induced to believe that they are playing an online ball-tossing game with two other partners. The cyberball task includes 'inclusion' phases during which the two other partners play with the participant, and 'exclusion' phases during which they throw the ball only to each other, thus excluding the participant. The comparison of exclusion versus inclusion phases is assumed to capture sensitivity to social rejection.

Functional magnetic resonance imaging (fMRI) studies assessing differences between exclusion and inclusion phases have consistently

reported activations within the anterior cingulate cortex (ACC). The ACC is classically divided into a dorsal portion (dACC) and a ventral portion (vACC). The dACC, also called midcingulate cortex (MCC, Vogt, 2004), corresponds to the supracallosal portion of the cingulate, it comprises Brodmann areas 24a', 24b', 24c', 24d, 32' and 33, and it could further be divided into an anterior (aMCC) and posterior portions (pMCC). The ventral portion lying anterior and ventral to the corpus callosum comprises Brodmann areas 24a, 24b, 24c, 25, 32 and 33, and it could further be divided into pregenual (pgACC) and subgenual (sgACC) subdivisions (Figure 1) (Vogt, 2009; Etkin *et al.*, 2011; Shackman *et al.*, 2011). These subdivisions were supported by regional differences in cytoarchitecture, connectivity and functions (Vogt, 2009). Neuroimaging studies reliably reported the involvement of dACC in high cognitive demands, such as conflict monitoring or error detection, whereas vACC was more specifically related in emotion processing, including the assessment of emotional information and the regulation of emotional responses. However, many recent studies challenged this functional bipolarity, showing that the aMCC contributed to the integration of cognitive and affective information, especially negative affect, pain and cognitive control (Etkin *et al.*, 2011; Shackman *et al.*, 2011; Spunt *et al.*, 2012).

The first fMRI study assessing the neural correlates of social pain with the cyberball task (Eisenberger *et al.*, 2003), which strongly impacted the scientific community, as revealed by the high number of citations ($n = 843$ in March 2014, Web of Science®), reported an activation of the aMCC. However, some researchers have challenged the specificity of this result as regards the aMCC, pointing out that differences between the two Cyberball conditions may relate to the violation of participants' expectations rather than to social rejection. Therefore, it was questioned whether the observed aMCC activation was truly related to social rejection rather than to expectancy violation. First, a

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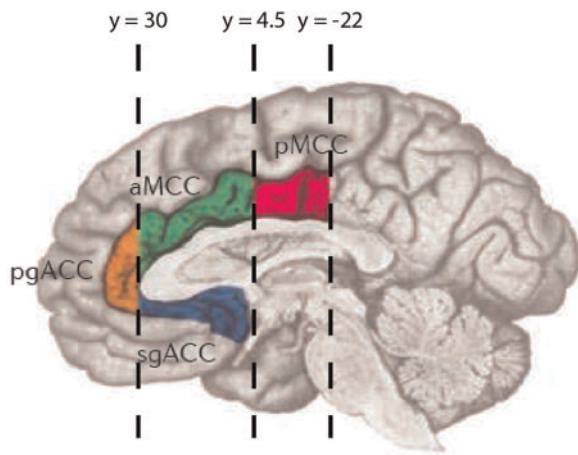


Fig. 1 Boundaries of ACC subdivisions. This figure was inspired by Shackman *et al.* (2011, Figure 1C). With the kind permissions of Nature Publishing Group and the corresponding author, Dr Alexander J. Shackman.

research team showed with a social feedback task that changes in pgACC activations were related to social feedback, whereas changes in aMCC activations were linked to expectancy violation (Somerville *et al.*, 2006). However, in this study, social acceptance was associated with greater pgACC activation than social rejection. Second, contrasting the Cyberball with a similar ball-tossing game in which rules are broken in the absence of social rejection, activation in the sgACC was related to social rejection, whereas activation in the aMCC activations was linked to expectancy violation (Bolling *et al.*, 2011a), thus raising the question of the functional role of the aMCC activations found in the seminal cyberball study (Eisenberger *et al.*, 2003). Finally, many other fMRI studies using the cyberball task reported exclusion-related ACC activations; however, these activations were described either in the dorsal part or in the ventral part. This was also true for fMRI studies assessing ACC activations during social pain with other experimental paradigms, such as the display of disapproving faces, negative social evaluation, grief during bereavement or relationship break. Furthermore, some studies reported deactivations in both ventral and dorsal parts of the ACC during social pain (Najib *et al.*, 2004; Somerville *et al.*, 2006; Kross *et al.*, 2007) and others described an enhanced activity in the vACC in response to positive rather than negative social feedback (Somerville *et al.*, 2006). Therefore, which are the ACC subdivisions involved in social pain remains debated.

The aim of the present study was to clarify this scientific debate by assessing whether one of the ACC divisions is preferentially involved in social pain. To achieve this goal, activation likelihood estimation (ALE), a voxel-based meta-analysis method, was used to provide a quantitative estimate of the probability of activation across fMRI studies. Moreover, regression analyses were performed to identify demographic variables or paradigm differences that may contribute to the discrepancy of ACC activations across fMRI studies. This point is particularly crucial for future studies of social pain and its neural underpinnings.

METHODS

Literature search and study selection

MEDLINE and PsycINFO databases were searched through March 2013, without limits on the year of publication, using the keywords 'cyberball', 'social exclusion', 'social rejection', 'ostracism', 'social negative evaluation', 'social feedback', 'evaluative threat', 'disapproving faces', 'romantic rejection', 'bereavement', 'social pain', 'magnetic

resonance imaging', 'MRI', 'neuroimaging', 'functional magnetic resonance imaging', 'fMRI' or 'functional neuroimaging'. After the removal of duplicate articles, 241 unique articles were identified. Studies were then considered for inclusion if they (i) were published in English in a peer-reviewed journal, (ii) used fMRI methods, (iii) used an experimental task exploring social pain, as previously defined (Eisenberger, 2012b), (iv) reported results for whole-brain contrasts for social pain, or whole-brain regression analyses with self-reported distress during social pain in healthy participants, and (v) reported significant functional changes within the ACC. Social pain-related activations described in clinical samples were not considered for inclusion. Studies reported group differences in healthy participants, for example, in individuals with low vs. high self-esteem, were included; however, they were specifically pointed out and sensitivity analyses were performed to make sure they did not drive the main results of the meta-analysis (Table 1). All articles written by a given research group were carefully scrutinized for ensuring that data were not entered twice in the meta-analysis. In this case, we used data from the largest study population and excluded the others (Eisenberger *et al.*, 2007b; O'Connor *et al.*, 2009; Koenigsberg *et al.*, 2010; Sebastian *et al.*, 2010a; Slavich *et al.*, 2010; Somerville *et al.*, 2010; Cribben *et al.*, 2012; Lindquist *et al.*, 2012). Some articles with subject overlap (Eisenberger *et al.* 2007a, b, c; Way *et al.*, 2009; Bolling *et al.* 2011b, c or Onoda *et al.* 2009, 2010, for instance), which provided complementary information, were not formally excluded and described in Table 1; however, they were never entered into a same analysis (Table 1). For example, in the two papers published by Onoda *et al.* (2009, 2010), the first one allowed the inclusion of foci during social pain analyses (2010) and the other one was included because results from regression analyses were reported (2009). Figure 2 depicted the process of article selection in details. Therefore, the literature search conducted to the inclusion of 46 studies corresponding to 940 healthy subjects (Eisenberger *et al.*, 2003, 2007a, c, 2009, 2011; Gündel *et al.*, 2003; Najib *et al.*, 2004; Somerville *et al.*, 2006; Burklund *et al.*, 2007; Kross *et al.*, 2007, 2011; O'Connor *et al.*, 2008; Rilling *et al.*, 2008; Freed *et al.*, 2009; Kersting *et al.*, 2009; Krill and Platek, 2009; Masten *et al.*, 2009, 2011a, b, c, 2012; Onoda *et al.*, 2009, 2010; Takahashi *et al.*, 2009; Wager *et al.*, 2009a, b; Way *et al.*, 2009; DeWall *et al.*, 2010, 2012; Fisher *et al.*, 2010; Gunther-Moor *et al.*, 2010; Slavich *et al.*, 2010; Bolling *et al.*, 2011a, b, c, 2012; Karremans *et al.*, 2011; Sebastian *et al.*, 2011a; Gradin *et al.*, 2012; Gyurak *et al.*, 2012; Kawamoto *et al.*, 2012; Maurage *et al.*, 2012; Moor *et al.*, 2012; Premkumar *et al.*, 2012; Lelieveld *et al.*, 2013; Phan *et al.*, 2013) (Table 1).

Data extraction

For each study, we systematically identified the used standardized atlas (Montreal Neurological Institute [MNI] or Talairach Space). Each included study reported at least one significant focus in the ACC. For each ACC focus, we extracted the coordinates of the corresponding coordinates (x, y, z in a standardized atlas), volumes and the standardized precipitation index (z-score or t-values). Because some coordinates may appear ambiguous regarding their belonging to the ACC or adjacent cortices, Talairach Client was used to make sure that they were ACC coordinates (Talairach Client, version 2.4.3, www.talairach.org) (Lancaster *et al.*, 1997, 2000). MNI coordinates were converted to Talairach space using the Lancaster transform (icbm2tal) (Laird *et al.*, 2010). Furthermore, demographic and experimental variables including age, gender and handedness, and the duration and the number of exclusion conditions in cyberball task were extracted for each study when available.

Table 1 Included fMRI studies

Study	Experimental task	Number of subjects	sgACC	pgACC	aMCC	pMCC
fMRI studies reporting functional ACC changes during social pain						
Eisenberger <i>et al.</i> , 2003	Cyberball	13			(+)	
Gündel <i>et al.</i> , 2003	Grief—Bereavement	8			(+)	
Najib <i>et al.</i> , 2004	Grief—Rejection in love	9			(−)	
Somerville <i>et al.</i> , 2006	Social evaluation	22		(−)		
Kross <i>et al.</i> , 2007	Rejection images	20			(+)	
O'Connor <i>et al.</i> , 2008	Grief—Bereavement	12		(+)	(+)	
Rilling <i>et al.</i> , 2008	Unreciprocated cooperation	20			(+)	
Masten <i>et al.</i> , 2009 ^a	Cyberball	23	(+)			
Krill and Platek, 2009	Cyberball	14		(+)	(+)	
Way <i>et al.</i> , 2009 ^a	Cyberball	31			(+)	
Kersting <i>et al.</i> , 2009	Grief—Bereavement	12		(+)		(+)
Takahashi <i>et al.</i> , 2009	Social evaluation	19				(+)
Wager <i>et al.</i> , 2009a	Social evaluative threat	24		(+)		
Wager <i>et al.</i> , 2009b	Social evaluative threat	18			(+)	
DeWall <i>et al.</i> , 2010 ^b	Cyberball	15			(+)	(+)
Onoda <i>et al.</i> , 2010 ^c	Cyberball	26		(+)	(+)	
Fisher <i>et al.</i> , 2010	Rejection in love	15		(+)		
Gunther-Moor <i>et al.</i> , 2010 ^d	Social evaluation	16	(+)			
Kross <i>et al.</i> , 2011	Rejection in love				(+)	
Bolling <i>et al.</i> , 2011a	Cyberball	26	(+)			
Bolling <i>et al.</i> , 2011b ^a	Cyberball	24		(+)		
Bolling <i>et al.</i> , 2011c ^a	Cyberball	26		(+)		
Masten <i>et al.</i> , 2011a ^e	Cyberball	17		(+)		
Masten <i>et al.</i> , 2011b	Cyberball	18		(+)		
Sebastian <i>et al.</i> , 2011a	Cyberball	35	(+)			
Karremans <i>et al.</i> , 2011	Cyberball	15	(+)			
Gradin <i>et al.</i> , 2012	Cyberball	16		(+)		
Maurage <i>et al.</i> , 2012 ^f	Cyberball	22		(+)		
Moor <i>et al.</i> , 2012 ^f	Cyberball	53	(+)	(+)		
Masten <i>et al.</i> , 2012	Cyberball	21			(+)	
Bolling <i>et al.</i> , 2012 ^g	Cyberball	24	(+)			
Kawamoto <i>et al.</i> , 2012 ^f	Cyberball	21			(+)	
Premkumar <i>et al.</i> , 2012 ^h	Rejection images	12				(+)
Gyurak <i>et al.</i> , 2012 ⁱ	Rejection images	23		(+)		
Lelieveld <i>et al.</i> , 2013 ^f	Cyberball	30			(+)	
Phan <i>et al.</i> , 2013 ^j	Social threat signals	19			(+)	
fMRI studies reporting whole brain regressions with self-reported distress in the ACC						
Eisenberger <i>et al.</i> , 2003 ^f	Cyberball	13		(+)	(+)	
Eisenberger <i>et al.</i> , 2007a ^{a,f}	Cyberball	32		(+)	(+)	
Eisenberger <i>et al.</i> , 2007c ^{a,f}	Cyberball	32			(+)	
Burklund <i>et al.</i> , 2007 ⁱ	Disapproving faces	16		(+)	(+)	
Kross <i>et al.</i> , 2007	Rejection images	20			(−)	
Eisenberger <i>et al.</i> , 2009	Cyberball	10			(+)	
Onoda <i>et al.</i> , 2009 ^f	Cyberball	26		(+)	(+)	
Masten <i>et al.</i> , 2009 ^a	Cyberball	23	(+)			
Wager <i>et al.</i> , 2009b ^k	Social evaluative threat	18		(+)		
Freed <i>et al.</i> , 2009 ^l	Grief—Bereavement	20			(+)	
Masten <i>et al.</i> , 2011b ^m	Cyberball	18		(+)	(+)	
Masten <i>et al.</i> , 2011c ^{a,e,n}	Cyberball	20	(+)	(+)		
Eisenberger <i>et al.</i> , 2011 ^{f,o}	Social evaluation	19			(+)	
Masten <i>et al.</i> , 2012	Cyberball	21				(+)
DeWall <i>et al.</i> , 2012	Cyberball	25			(+)	

^aThese articles with subject overlap were not included in the same analysis.

^bACC activations were observed when comparing a group under placebo vs a group under actaminophen.

^cACC activations were observed when comparing subjects with low vs high trait self-esteem.

^dsgACC activations for the exclusion > acceptance contrast were observed in a sub-group of 19–25 year olds subjects, and not in children and adolescents.

^eThe authors reported activations in the sgACC; however, ACC activations refer to pgACC according to the ACC delineation used in the present meta-analysis.

^fThe authors reported activations in the dorsal ACC; however, ACC activations refer to both pgACC and aMCC according to the ACC delineation used in the present meta-analysis.

^gReported coordinates corresponded to the maximum signal change of a large cluster extending to the medial prefrontal cortex and dorsal ACC.

^hACC changes were described between groups with low vs high schizotypy during a rejection > neutral contrast.

ⁱACC activation was related to the interaction term of self-esteem and attentional control during a rejection > negative contrast.

^jACC activation was related to the difference between social phobics and controls during a angry > happy contrast.

^kLpgACC activation was described a mediator of subjective anxiety changes across time.

^lCorrelations were observed for an intrusiveness score.

^mPositive correlations were observed between self-reported distress and sgACC activity and between observer-rated distress and aMCC activity.

ⁿCorrelations were observed for depressive symptoms.

^oNegative correlations were observed with state self-esteem.

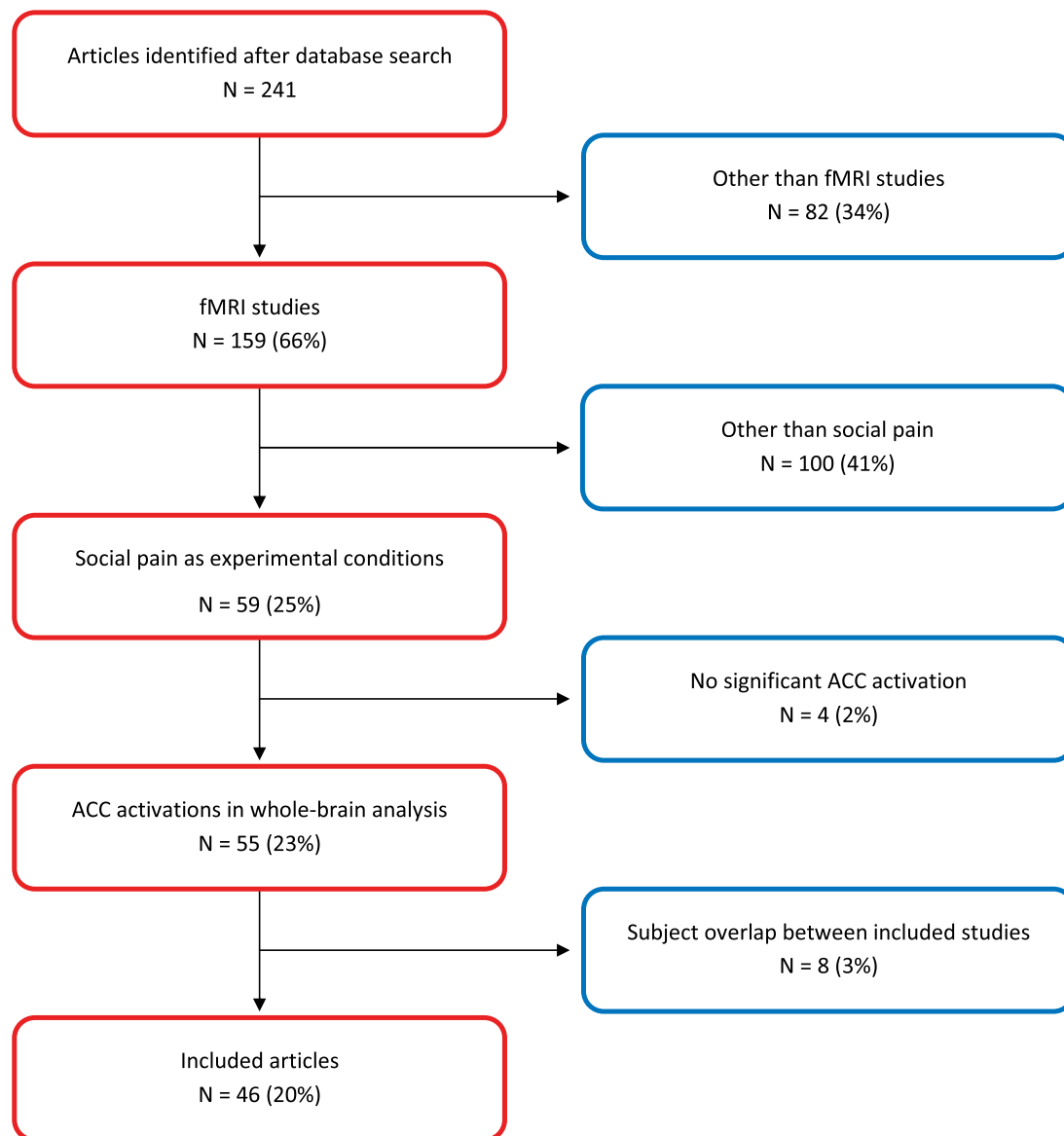


Fig. 2 Article selection process of fMRI studies of social pain.

Boundaries of ACC subdivisions

To accurately allocate activations within the ACC to a specific ACC subdivision, we used the following boundaries, as previously defined in the Talairach space (Vogt *et al.*, 2003; Vogt, 2009), (i) sgACC: $y < 30$, (ii) pgACC: $y > 30$, (iii) aMMC: $4.5 < y \leq 30$ and $z >> 0$ and (iv) pMMC: $-22 < y \leq 4.5$ and $z >> 0$, as depicted in Figure 1.

ALE meta-analyses

ALE meta-analyses were completed using Scribe (version 2.0), Sleuth (version 2.0.3) and GingerALE (version 2.2) software (www.brainmap.org) (Laird *et al.*, 2005; Eickhoff *et al.*, 2009, 2012; Turkeltaub *et al.*, 2012). We conducted ALE analyses: (i) including experimental contrasts assumed to capture social threat, exclusion or loss, and (ii) including ACC activations related to self-reported distress during social threat, exclusion or loss. Furthermore, since studies using the cyberball task represented 56% of all included studies, we conducted secondary analyses for cyberball studies reporting ACC activations during the exclusion > inclusion contrast or ACC activations related

to self-reported distress during this contrast or both. Statistical thresholds were set at a false discovery rate (FDR) corrected threshold of $P < 0.05$ with a minimum cluster size, as recommended by GingerALE (Eickhoff *et al.*, 2009). Because our meta-analysis was focused on one brain region, the identification of large cluster sizes that would not be helpful to specifically identify ACC subdivisions could be expected. Supplementary analyses with a more conservative statistical threshold ($P < 0.001$, FDR-corrected) were therefore performed. We used Mango (Multi-image Analysis GUI, University of Texas, Health Science Center) for viewing ALE map overlaid onto a high-resolution brain template generated by the International Consortium for Brain Mapping (Kochunov *et al.*, 2002).

Regression analyses

To test whether the ventro-dorsal gradient of ACC activations was explained by the demographic variables (i.e. mean age and sex-ratio) or methodological differences (i.e. duration and number of exclusion conditions), simple linear regression analyses were performed with the reported ACC z-coordinate-values as the dependent variable and each

of the following independent variables: ages, sex, block durations and block iterations. A Bonferroni correction was used to reduce the risk of type I errors (P set at $0.05/4 = 0.0125$).

RESULTS

Social pain was associated with significant probabilities of activation within aMCC, pgACC and sgACC (Figure 3A, Table 2). Secondary analyses based on the inclusion of studies using the cyberball task revealed similar results (Figure 3B, Table 2). Similarly, self-reported distress was associated with significant likelihood activations in aMCC, pgACC and sgACC (Figure 3C, D, Table 2).

To attempt to disentangle the respective functions of these different ACC subdivisions and to identify which part of the ACC could be more specifically related to social distress rather than to other types of cognitive and emotional processing in response to a situation of social pain, an overlap map with both self-reported distress-related regression and social pain-related contrast was created (Figure 4). Overlaps were identified in sgACC, pgACC and aMCC.

Possible differences between cyberball studies and all other included studies were also examined by contrasting the corresponding ALE maps. Cyberball studies reported significantly less aMCC (BA 24: $x, y, z = 4, 10, 31, 320 \text{ mm}^3$) than all other included studies reporting contrasts for social pain. No significant difference between cyberball and other studies was observed regarding ACC activations related to self-reported distress. Finally, we contrasted ALE maps corresponding to children and to adults ($P_{\text{FDR}} < 0.05$). Probabilities of activations were significantly more enhanced within sgACC (BA25: $x, y, z = 5, 16, -4, 1376 \text{ mm}^3$) in children (9 studies) compared with adults (29 studies), whereas studies including adults exhibited higher probabilities of activations within pgACC than studies including children (BA32: $x, y, z = 4, 34, 16, 232 \text{ mm}^3$).

The ventro-dorsal gradient of ACC activations was not explained by demographical variables. Indeed, no significant relationship between ACC z-coordinate-values and age ($r = -0.02, P = 0.83$ for social pain-related contrast; $r = -0.06, P = 0.82$ for self-reported distress-related regression) or gender ($r = 0.12, P = 0.74$ for social pain-related contrast; $r = 0.28, P = 0.28$ for self-reported distress-related regression) was found. Furthermore, no significant relationship was observed between ACC z-coordinate-values and the number of repeated blocks ($r = -0.47, P = 0.08$ for social pain-related contrast; $r = -0.47, P = 0.11$ for self-reported distress-related regression). However, linear

regression analyses revealed a positive and significant correlation between the duration of the exclusion conditions and the ACC z-coordinate-values reported for both the exclusion > inclusion contrast ($r = 0.73, P < 0.01$, corrected, Figure 5A) and for the self-reported distress during the cyberball task ($r = 0.80, P < 0.01$, corrected, Figure 5B). Finally, to strengthen the confidence in the present results, we measured partial correlations between ACC z-coordinate-values and the duration of the exclusion conditions, while controlling the effect of age, sex or the number of blocks. This relationship remained significant with age ($r = 0.63, P < 0.05$ for social pain-related contrast; $r = 0.80, P < 0.01$ for self-reported distress-related regression), sex ($r = 0.73, P < 0.01$ for social pain-related contrast; $r = 0.75, P < 0.01$ for self-reported distress-related regression) and the number of repeated blocks ($r = 0.61, P < 0.05$ for social pain-related contrast; $r = 0.70, P < 0.05$ for self-reported distress-related regression) as control variables. Thus, longer durations of the exclusion conditions were associated with more dACC activity, whereas shorter durations were associated with more vACC activity, independently of the mean age and the proportion of male/female of the included samples and the number of blocks used during the cyberball task.

Leave-one-out sensitivity analyses by repeating the analyses with the consecutive exclusion of each study showed that our main results were

Table 2 Clusters of significant likelihood for ACC activations

	Brodmann areas	Talairach coordinates			Volume (mm ³)	Maximum ALE z value (×10 ³)
		x	y	z		
Social pain (33 studies, 45 foci, 725 subjects)						
$P_{\text{FDR}} < 0.05$	25/32	4	36	−4	12 512	30.2
$k = 1056 \text{ mm}^3$	24/32	8	24	24	7200	22.2
$P_{\text{FDR}} < 0.001$	24/32	4	36	−4	6024	30.2
$k = 16 \text{ mm}^3$	24/32	8	24	24	2240	22.2
	25	0	8	−2	304	15.5
	32	−8	18	42	304	14.4
Social rejection in cyberball studies (19 studies, 27 foci, 467 subjects)						
$P_{\text{FDR}} < 0.05$	25/32	4	36	−4	7464	29.4
$k = 648 \text{ mm}^3$	32	10	14	38	1656	12.1
	32	−4	42	20	1272	14.9
	32	8	22	26	1200	15.9
$P_{\text{FDR}} < 0.001$	32	4	36	−4	3480	29.4
$k = 8 \text{ mm}^3$	32	8	22	26	368	15.9
	32	−4	42	12	320	14.9
	25	−2	8	−2	304	15.5
	24	0	8	28	304	15.3
	32	10	14	38	168	12.1
Self-reported distress during social pain (13 studies, 20 foci, 259 subjects)						
$P_{\text{FDR}} < 0.05$	24/32	10	32	−2	5304	16.7
$k = 464 \text{ mm}^3$	24/32	−8	18	−6	1840	10.3
	32	−6	10	46	1472	8.9
$P_{\text{FDR}} < 0.001$	32	14	28	32	680	12.5
$k = 8 \text{ mm}^3$	24	10	32	−2	456	16.7
	25	−8	22	−10	64	8.9
	32	−6	10	46	64	8.9
	24	−8	8	36	32	8.6
Self-reported distress during social rejection (8 studies, 9 foci, 160 subjects)						
$P_{\text{FDR}} < 0.05$	24/25	−8	22	−10	1864	10.3
$k = 296 \text{ mm}^3$	24/32	−6	10	46	1824	8.9
	8	−10	30	38	1152	14.9
	24	10	32	−2	480	8.1
	6	−6	−12	54	456	8.5
$P_{\text{FDR}} < 0.001$	8	−10	30	38	432	14.9
$k = 8 \text{ mm}^3$	25	−8	22	−10	216	10.3
	32	−6	10	46	96	8.9
	24	−8	8	36	64	8.6
	24	10	32	−2	16	8.1

k values are the recommended minimum cluster sizes (Eickhoff et al., 2009).

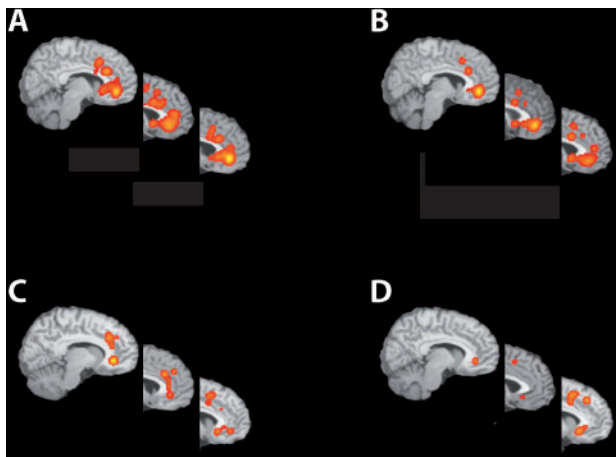


Fig. 3 ALE maps with $P_{\text{FDR}} < 0.05$. Probabilities of ACC activations during social threat, exclusion or loss (A) and for the 'exclusion > inclusion' contrast during the cyberball task (B). Probabilities of ACC activations related to self-reported distress during social threat, exclusion or loss (C), and during the cyberball task (D).

not driven by one outlier study. Specifically, both vACC and dACC activations remained significant whatever the study excluded. Additional sensitivity analyses consisting in the repetition of ALE analyses were conducted with the exclusion of (i) studies reported group differences (DeWall *et al.*, 2010; Onoda *et al.*, 2010; Premkumar *et al.*, 2012; Phan *et al.*, 2013) (ii) studies marked with superscript footnote indicators 'b–d, g–j, l–n' in Table 1. Sensitivity analyses showed no marked difference regarding the overall findings.

Finally, we conducted supplementary ALE analyses by including all reported activations, i.e. intra-ACC and extra-ACC activations. Studies that did not report ACC activations were also included. Results are available in [Supplementary Materials](#).

DISCUSSION

The present meta-analysis shows that three parts of the ACC, namely sgACC, pgACC and aMCC, are involved in social rejection and more generally in social pain. Self-reported distress during exposure to social pain is robustly associated with neural activity in sgACC, pgACC and aMCC. Neural activity associated with exposure to social pain and neural activity associated with self-reported distress during such exposure overlapped in sgACC, pgACC and aMCC. Furthermore, studies with children exhibited significantly greater or more frequent activations within sgACC than studies with adults, whereas studies with

adults exhibited greater or more frequent activations within pgACC than studies with children, suggesting that the involvement of ACC subregions may depend on development. Finally, the cyberball task elicited less activation of the aMCC, the most dorsal part of the ACC involved in social pain, than other experimental paradigms. Other methodological differences may contribute to the ventro-dorsal gradient of ACC activations during the cyberball task for both social rejection-related contrasts and the self-reported distress-related regressions. Indeed, longer durations of exclusion were associated with more dACC activity, whereas shorter durations were associated with more vACC activity, independently of age and sex. Many factors, including cognitive and emotional processes, may contribute to this relationship between the duration of inclusion-exclusion phases in cyberball and the ventro-dorsal gradient of ACC activations during the cyberball task.

Owing to the role of the aMCC in the affective component of physical pain (Shackman *et al.*, 2011), the seminal observation of its activation during the exclusion phase of the cyberball task (Eisenberger *et al.*, 2003) led to fascinating hypotheses about the links between social and physical pain (Panksepp, 2003). These hypotheses have been systematically tested and the results so far are consistent with the view that social and physical pain may share similar neural underpinnings, including the anterior insula and the aMCC (Eisenberger, 2012a). The aMCC as a shared neural correlate for social and physical pain was mainly questioned through the different possible interpretations concerning the psychological correlates of the exclusion phase during the cyberball task. Indeed, some authors proposed that this phase elicited cognitive reactions linked to violated expectations of inclusion rather than social pain *per se* (Somerville *et al.*, 2006; Bolling *et al.*, 2011a). Therefore, they attempted to dissociate the neural correlates of social pain from those of expectancy violation. For example, comparing the cyberball task with a similar ball-tossing game in which rules are broken in the absence of social rejection, activation in the sgACC was related to social rejection, whereas activation in the aMCC was linked to expectancy violation (Bolling *et al.*, 2011a). However, when comparing social rejection with rule violation, the authors observed activations within sgACC and pMCC (Bolling *et al.*, 2011a). An event-related fMRI study has also attempted to discriminate the neural correlates of social pain from those of expectancy violation during the cyberball task (Kawamoto *et al.*, 2012). To address this issue, the authors have added an overinclusion condition trying to make expectancy violation constant across conditions of interest (i.e. overinclusion and exclusion). They reported greater activity within dACC during exclusion, relative to overinclusion, whereas subjects

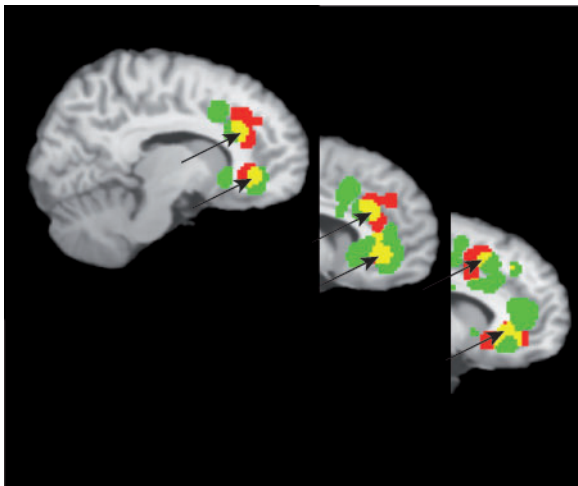


Fig. 4 Overlap of ALE maps corresponding to self-reported distress-related regression (red) and social pain-related contrast (green). Yellow indicates overlap between both ALE maps.

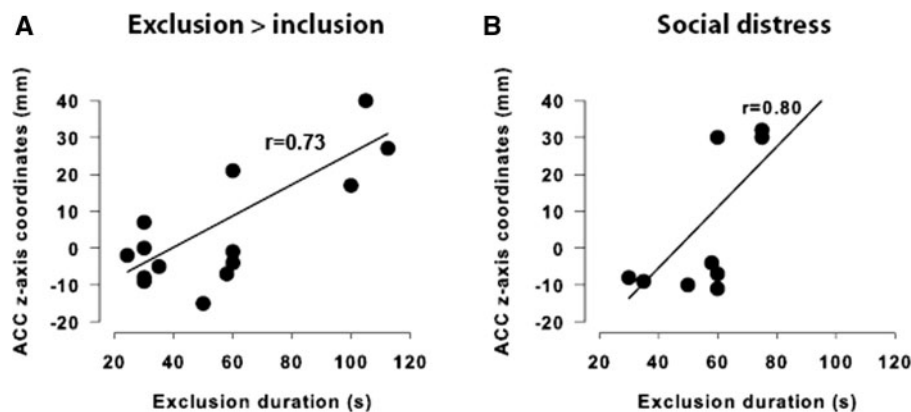


Fig. 5 The duration of the exclusion phase contributed to the ventro-dorsal gradient of ACC activations during the cyberball task. There was a positive relationship between the duration of the exclusion phase and the coordinate along the z-axis of activations corresponding to the 'exclusion > inclusion' contrast ($r = 0.73$, $P < 0.05$) (A) and to the self-reported distress ($r = 0.80$, $P < 0.05$) (B), respectively, which suggested that long exclusion blocks involve the dorsal division of ACC, whereas short exclusion blocks involve the ventral division of ACC.

reported more surprise during overinclusion than exclusion, suggesting that dACC activity might be specifically associated with social exclusion. Future studies are required to completely rule out the expected violation-related dACC activity during the cyberball task. Overinclusion conditions may appear relevant for controlling possible expectancy violation processes during the cyberball task, replicated results are needed, especially by inserting overinclusion in a block-designed cyberball task.

A study using intracranial electroencephalography associated with the cyberball task demonstrated that sgACC, the most ventral part of the ACC, responded to social exclusion (Cristofori *et al.*, 2013). The latency of the sgACC response decreased throughout the successive phases of exclusion, suggesting that the sgACC was sensitive to the repetition of exclusion and could learn to rapidly signal emotional and cognitive processes related to the situation of social rejection (Cristofori *et al.*, 2013). On the basis of studies showing sgACC activations during negative stimuli (George *et al.*, 1995; Haas *et al.*, 2007) and its connections with the amygdala and periaqueductal gray matter (Neafsey *et al.*, 1993), some authors have proposed that sgACC activations during social pain might be related to the affective experience of social pain (Sebastian *et al.*, 2011a). Although the specific role of sgACC in social pain has still been not elucidated and disambiguated from more dorsal parts of the ACC, the stronger negative feelings associated with social rejection reported in adolescence supported this interpretation (Sebastian *et al.*, 2010b, 2011a). Indeed, we showed that children exhibited sgACC to a greater extent than adults during social pain, in accordance with prior fMRI studies that assessed age effects in social pain (Masten *et al.*, 2009; Gunther-Moor *et al.*, 2010; Sebastian *et al.*, 2011a). Although these results suggest that the sgACC may also play a critical role in the appraisal or expression of emotional and cognitive processes involved in social rejection from a neurodevelopmental perspective, a recent review rather argued for a regulatory role of sgACC in negative emotions (Etkin *et al.*, 2011). Finally, the findings by Cristofori *et al.* (2013) were also supported by recent fMRI studies that also reported sgACC activations during the exclusion phases of the cyberball task in adults (Karremans *et al.*, 2011; Bolling *et al.*, 2011a, 2012). These studies, by showing that the cyberball task involved the sgACC in social rejection, with or without discriminating the expectancy violation as reported by Bolling *et al.* (2011a), lead to suggest that other parameters should be considered for explaining the discrepancy across fMRI results.

Since correlations with self-reported distress did not allow us to discriminate the functional roles of aMCC and most ventral parts of the ACC, i.e. sg and pgACC, we conducted regression analyses in an attempt to explain ventro-dorsal gradient of ACC activations observed during social rejection. Our regression analyses suggest that the discrepancy across fMRI studies using the cyberball task may be explained by some differences in methodological approaches, as previously hypothesized (Sebastian *et al.*, 2011a, b). Specifically, shorter inclusion-exclusion phases promoted the involvement of the vACC, whereas longer inclusion-exclusion phases promoted the involvement of the dACC, independently of age, sex and the repetition of exclusion. Many hypotheses may be advanced for explaining this relationship. Long phases of inclusion increased the experience of observation and interaction with both other players and thus may have led to strong predictive expectations (Burgoon and Jones, 1976). The subsequent exclusion phase may therefore lead to expectancy violations to a greater extent. However, during a long exclusion phase, expectancy violation should diminish, whereas social distress may persist throughout the block. When blocks were shorter, they were usually repeated multiple times, which may have reduced the level of belief in the cyberball task. As suggested, these methodological differences may affect the psychological processes involved during the cyberball task

and, therefore, their neural correlates. Furthermore, this relationship could be explained by other confounded variables, which could not be taken into account in the present meta-analysis. For example, during the exclusion phase, participants could be directly excluded (Bolling *et al.*, 2011a; Sebastian *et al.*, 2011a; Moor *et al.*, 2012) or they could receive a limited number of throws before being excluded (Eisenberger *et al.*, 2003, 2007; Masten *et al.*, 2009, 2011a, b; Maurage *et al.*, 2012). When fMRI paradigms included several blocks of inclusion and exclusion, these blocks may be displayed either in an alternating order (Bolling *et al.*, 2011a; Maurage *et al.*, 2012) or in a randomized order (Sebastian *et al.*, 2011a). Although it seems likely that those experimental differences may affect the results observed across fMRI studies, their respective impacts on exclusion-related activations remain unclear and should further be explored. Resolving the impact of these methodological issues on ACC activity during the cyberball task would help to better understand the specific role of ACC subregions in social exclusion. Finally, this relationship between the duration of condition and the ventro-dorsal gradient of ACC activations during social rejection suggests a possible temporal dynamic between sgACC, pgACC and aMCC. It would be interesting for future research to investigate the time course of these ACC divisions or to test their modes of connectivity during social rejection.

It is noteworthy that the present results are consistent with the critical role of both sgACC and social rejection in major depression. First, among adverse events that may eventually precipitate major depression, those involving a social rejection component are of particular relevance and yield a greater impact (Kendler *et al.*, 2003). Second, sgACC (including Brodmann area 25 and parts of 24 and 32) plays a central role in the pathophysiology of major depression as strongly suggested by both anatomical and functional changes (Hamani *et al.*, 2011), as well as by its emerging potential role as a surgical target for deep brain stimulation (Mayberg *et al.*, 2005). In the context of the

Highlights

Outcomes

- Neural activity during social pain involves aMCC, pgACC and sgACC
- Neural activity associated with self-reported social distress involves aMCC, pgACC and sgACC
- The likelihood of activations within ACC subregions varies throughout development
- The likelihood of activations within ACC subregions varies with methodological variables

Perspectives

- Understanding the temporal dynamic and the connectivity of ACC subregions during social pain
- Understanding the developmental variations of the contribution of ACC subregions in social pain
- Resolving methodological issues contributing to the variations of likelihood of activations within ACC subregions
- Defining the role of sgACC in the relationship between social pain and depression

Fig. 6 Highlights: main outcomes and perspectives.

cyberball task, activation of the sgACC during exclusion phases among adolescents predicted increase in depressive symptoms after a 12 month follow-up (Masten et al., 2011c). Our results are thus consistent with a role of the sgACC activation as biological mechanism linking social rejection with liability for major depression.

In conclusion, the present meta-analysis supports and extends previous findings concerning the neural correlates of social pain and, more specifically, of social rejection during the cyberball task (Figure 6). We showed that both the vACC and the dACC were involved in social pain. Many factors may affect this ventro-dorsal gradient, such as age, the used task or the length of exclusion condition. In particular, the condition length may contribute to the discrepancy across fMRI studies using the cyberball task. It remains to be determined which psychological correlates are associated with this experimental parameter. In perspective, considering the critical importance of the sgACC in major depression, we propose that the cyberball task may be particularly relevant to study the neural correlates of social rejection in such clinical context.

Conflict of Interest

None declared.

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