Early and late neural correlates of mentalizing: ALE meta-analyses in adults, children and adolescents

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Abstract

The ability to understand mental states of others is referred to as mentalizing and enabled by our Theory of Mind. This social skill relies on brain regions comprising the mentalizing network as robustly observed in adults but also in a growing number of developmental studies. We summarized and compared neuroimaging evidence in children/adolescents and adults during mentalizing using coordinate-based activation likelihood estimation meta-analyses to inform about brain regions consistently or differentially engaged across age categories. Adults ($N = 5286$) recruited medial prefrontal and middle/inferior frontal cortices, precuneus, temporoparietal junction and middle temporal gyri during mentalizing, which were functionally connected to bilateral inferior/superior parietal lobule and thalamus/striatum. Conjunction and contrast analyses revealed that children and adolescents ($N = 479$) recruit similar but fewer regions within core mentalizing regions. Subgroup analyses revealed an early continuous engagement of middle medial prefrontal cortex, precuneus and right temporoparietal junction in younger children (8–11 years) and adolescents (12–18 years). Adolescents additionally recruited the left temporoparietal junction and middle/inferior temporal cortex. Overall, the observed engagement of the medial prefrontal cortex, precuneus and right temporoparietal junction during mentalizing across all ages reflects an early specialization of some key regions of the social brain.

Key words: mentalizing; functional neuroimaging; development; children; theory of mind; activation likelihood estimation

Introduction

A fundamental premise of our everyday social life is the ability to understand and acknowledge the emotions and intentions of people around us. The constant observation, decoding and understanding of the mental states of ourselves and others is reflected in our mentalizing skills and enabled by our Theory of Mind (Frith and Frith, 2007). Mentalizing skills have shown to be positively associated with healthy social functioning (Slaughter *et al.*, 2015). Atypical mentalizing skills, however, have been described for several neurodevelopmental psychiatric disorders, including autism spectrum disorders, conduct disorder, depression, schizophrenia or borderline traits (Baron-Cohen *et al.*, 1997; Kerr *et al.*, 2003; Sharp, 2008; Zobel *et al.*, 2010; Moran *et al.*, 2011; Sharp *et al.*, 2011; Kronbichler *et al.*, 2017). Amongst these, hypermentalizing (e.g. borderline personality disorder), reduced mentalizing (e.g. psychopathy) or altered mentalizing skills (e.g. conduct disorder) have been reported (Blair *et al.*, 2004; Sharp *et al.*, 2011). Given their

daily critical role and importance for clinical diagnostics, mentalizing concepts have been key targets of different therapy settings (Björgvinsson and Hart, 2006; Fonagy and Allison, 2014; Fonagy *et al.*, 2017).

The foundation for mature mentalizing skills is laid early in life (Baillargeon *et al.*, 2010). For example, mothers' use of mental state language with their 6-month-old infants has been shown to predict children's later Theory of Mind performance (Meins *et al.*, 2002, 2003). Similarly, false belief tasks during which basic inferences are used to predict other people's intentions can already be employed in infancy (Knudsen and Liszkowski, 2012). Major conceptual improvements in mentalizing skills are suggested to occur around 3 to 6 years of age (Wellman *et al.*, 2001). However, mentalizing skills continue to mature throughout childhood and adolescence (Blakemore, 2008; Crone and Dahl, 2012; Crone and Steinbeis, 2017). Across age and skill levels, individuals learn to mentalize in a flexible and adaptive manner, allowing the

interpretation of increasingly complex social situations (Korkmaz, 2011).

The neural correlates of mentalizing in adulthood have been studied through various functional magnetic resonance imaging (fMRI) paradigms. Common implementations of mentalizing in fMRI paradigms include the false belief task (Mitchell, 2007; Tamnes *et al.*, 2010), Frith–Happé animations (Moriguchi *et al.*, 2006; Gobbini *et al.*, 2007) or the Reading the Mind in the Eyes Test (Gallagher *et al.*, 2000; Mascaro *et al.*, 2013). Other studies have implemented paradigms more broadly related to mentalizing processes, for example, through the study of self-referential knowledge (e.g. Ochsner *et al.*, 2005; Pfeifer *et al.*, 2007) or by motivation or mental state attributions underlying body movements (Spunt and Lieberman, 2012; Wurm and Schubotz, 2018). Overall, past evidence has identified core regions of the social brain during mentalizing in adults, including medial prefrontal cortex, bilateral temporoparietal junction, precuneus, inferior frontal gyri and the temporal lobes (Kliemann and Adolphs, 2018). More precisely, most studies have revealed consistent increases in brain activation during mentalizing in the medial prefrontal cortex and bilateral temporoparietal junction (summarized by meta-analyses: Van Overwalle, 2009; Mar, 2011; Schurz *et al.*, 2014; van Veluw and Chance, 2014; Molenberghs *et al.*, 2016). Additionally, areas including the posterior superior temporal sulci and gyri, temporal poles, precuneus and inferior frontal gyri (Mar, 2011; Molenberghs *et al.*, 2016), as well as anterior (Molenberghs *et al.*, 2016) and posterior (Mar, 2011) cingulate cortices and middle temporal gyri (van Veluw and Chance, 2014), were identified by some but not all studies. Differences in study reports have been suggested to result from variations in task choice, which may require further cognitive processes (Mar, 2011; van Veluw and Chance, 2014; Molenberghs *et al.*, 2016). Furthermore, in adults, connectivity between mentalizing regions (including temporoparietal junction, precuneus and medial prefrontal cortex) and insula, precentral and postcentral gyri and ventrolateral prefrontal cortex has been reported (Burnett and Blakemore, 2009; Lombardo *et al.*, 2010; Atique *et al.*, 2011; Schuwerk *et al.*, 2014). fMRI studies of mentalizing in children are more scarce compared to work conducted in adults. However, in line with technical and practical advances (Raschle *et al.*, 2012; Bednarz and Kana, 2018; Vijayakumar *et al.*, 2018), knowledge on early neural correlates of mentalizing continues to accumulate. Existing developmental studies of mentalizing indicate an early specialization and potential continuous engagement of some core regions associated with mentalizing in children starting around 3 (Richardson *et al.*, 2018; Richardson and Saxe, 2020) to 5 years of age (Gweon *et al.*, 2012) for regions including medial prefrontal cortex, temporoparietal junction and precuneus. Similarly, activation increases in regions including temporoparietal junction, precuneus, inferior parietal lobe and superior temporal sulci were detected in children aged 8–13 years (e.g. Kobayashi *et al.*, 2007; Moriguchi *et al.*, 2007; Yokota *et al.*, 2013; Mukerji *et al.*, 2019). To date, only few studies have directly investigated developmental effects for the neural correlates of mentalizing using longitudinal designs (Schulte-Rüther *et al.*, 2012; Overgaauw *et al.*, 2015). Such studies have detected stable activation in core regions for mentalizing, including medial prefrontal cortex, temporoparietal cortex, precuneus and superior/middle temporal and fusiform gyri in adolescents aged 12–18 (Schulte-Rüther *et al.*, 2012) and in right superior temporal sulcus and inferior frontal gyrus adolescents aged 12–19 (Overgaauw *et al.*, 2015). Overgaauw *et al.* (2015) additionally report nonlinear developmental trajectories for dorsal medial prefrontal cortex and linear decreases for right inferior frontal gyrus across age.

Cross-sectional studies have reported mentalizing-related activation increases in the medial prefrontal cortex when comparing children and adolescents of different ages. More specifically, medial and rostral prefrontal cortex activation during mentalizing has been reported for children aged 9–12 (Moriguchi *et al.*, 2007; Pfeifer *et al.*, 2007, 2009; Sommer *et al.*, 2010; Moor *et al.*, 2012) and adolescents up to 14 (Vetter *et al.*, 2014), 16 (Sebastian *et al.*, 2012) or 19 years (Burnett *et al.*, 2009). Neural activation for different age groups during mentalizing are also reported for the temporoparietal junction, but results vary. Some studies report continuous activation in temporoparietal junction [e.g. for children aged 5–9 (Gweon *et al.*, 2012) or 10–23 years (Moor *et al.*, 2012)]. Other studies detected increases in children aged 11–14 (Pfeifer *et al.*, 2009), while others report decreases in temporoparietal junction when comparing children to adults [e.g. 10–12 year olds (Sommer *et al.*, 2010)]. Similarly, age-related activation patterns for the inferior frontal gyri and temporal poles continue to be under investigation [e.g. in 10–19 year olds (Burnett *et al.*, 2009; Moor *et al.*, 2012)]. Overall, activation related to mentalizing in the medial prefrontal cortex, temporoparietal junction and precuneus in school-aged children and older are most commonly observed (Blakemore, 2008, 2012a,b; Saxe *et al.*, 2009; Crone and Dahl, 2012; Gweon *et al.*, 2012; Bowman *et al.*, 2019). Continuity and change within the neural regions for mentalizing are an intriguing subject of study (Blakemore *et al.*, 2007b; Sebastian *et al.*, 2012; Bowman *et al.*, 2019) but limited by the number of developmental studies available and by reduced power due to small-sample studies or lack of longitudinal work (Foulkes and Blakemore, 2018; Madhyastha *et al.*, 2018; Bowman *et al.*, 2019). Meta-analytic approaches allow the compilation of data deriving from various smaller, individual studies and may thereby overcome some of the associated power issues, allowing a more precise estimate of the present knowledge. Although meta-analytic work cannot inform about change across development, it may summarize the involvement of brain regions involved in mentalizing across certain age categories (Bowman *et al.*, 2019). While meta-analyses on mentalizing in adults exist (e.g. Schurz *et al.*, 2014; Molenberghs *et al.*, 2016), emerging studies in children and adolescents now further allow the conduction of coordinate-based meta-analyses in these age categories. Childhood and adolescence is a time of profound changes, and mentalizing abilities gain increasing importance in line with social maturation, the growing importance of peers and development of the own self. Novel evidence paralleling these processes may add to our understanding of biopsychosocial development in health and disease (e.g. Foulkes and Blakemore, 2018).

Here, we aimed to compile and compare existing knowledge on the neural correlates of mentalizing in children, adolescents and adults. Our main aims were to (i) perform a coordinate-based meta-analysis integrating data on neural activation and functional connectivity patterns during mentalizing in adults, (ii) compute a coordinate-based meta-analysis to integrate existing data on neural activation during mentalizing in children/adolescents and (iii) run a conjunction analysis to reveal common brain regions activated by adults and children/adolescents during mentalizing. Additionally, a contrast analysis in children/adolescents *vs* adults will be computed to detect distinct brain activation during mentalizing. Finally, (iv) follow-up analyses comparing children and adolescents allow for a first indication of neural patterns observed in younger children as compared to adolescents. Based on previous studies, we hypothesized mentalizing in adults to be associated with activation in medial prefrontal cortex, temporoparietal junction, precuneus, inferior frontal gyri and

temporal cortex (Van Overwalle, 2009; Mar, 2011; Schurz *et al.*, 2014; van Veluw and Chance, 2014; Molenberghs *et al.*, 2016). Moreover, functional connectivity between mentalizing regions (temporoparietal junction/posterior superior frontal sulcus and medial prefrontal cortex) and areas engaged during lower-level processes (Burnett and Blakemore, 2009; Lombardo *et al.*, 2010; Atique *et al.*, 2011; Schuwerk *et al.*, 2014) were expected. For children/adolescents, a similar but still developing activation pattern is hypothesized, reflected by the activation of some, but not all, areas reported in adults [e.g. engagement of medial prefrontal cortex but only emerging activation of the temporoparietal junction/superior temporal cortex (Blakemore, 2008, 2012a,b; Crone and Dahl, 2012)].

Methods
Literature search and study selection
We conducted systematic and standardized meta-analyses corresponding to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the revised Quality of Reporting of Meta-analyses statement (Moher *et al.*, 2009). Our main literature search was conducted through PubMed and included the keywords 'fMRI Theory of Mind' with and without the restriction to 'children' and/or 'adolescents' (search date in adults: 4 December 2018; in children/adolescents: 1 November 2019). Additionally, the reference lists of past meta-analyses and reviews investigating mentalizing were screened to identify any reports previously not detected (for details, see PRISMA flow diagram, **Supplementary Information 1**). Inclusion criteria for studies entering our meta-analyses were: whole-brain findings, coordinates provided in standard space [i.e. Talairach & Tournoux or Montreal Neurological Institute (MNI) space], contrasts targeting mentalizing and English publications. Studies based on region of interest (ROI) analyses or non-fMRI studies (e.g. electroencephalography and structural neuroimaging) and studies only yielding hypoactivations were excluded. The activation likelihood estimation methodology applied here does not allow the inclusion of null findings and does not account for differences in the thresholding of the studies entering the meta-analyses. A main goal of the present study was the investigation of brain activity related to mentalizing in adults and the comparison of these findings to evidence deriving from studies in children/adolescents. Studies that report brain activity deriving from mixed groups of adolescents and adults (without separate coordinates for adults and children/adolescents) were not included. Data from clinical research studies were only included for the healthy subgroups (i.e. coordinates on healthy control groups or main effects, representing brain activation equal to the clinical and control groups).

This procedure yielded a total of 228 studies of fMRI evidence for mentalizing with a total of 245 contrasts of interest and 5765 subjects. The adult meta-analysis included 206 studies with 2876 activation foci from 223 contrasts in 5286 subjects (Table 1; **Supplementary Information 2**). The meta-analysis on developmental neuroimaging studies of mentalizing in children/adolescents included 22 studies with 217 activation foci from 22 contrasts in 479 subjects (Table 2; **Supplementary Information 3**).

Meta-analytic methods
Activation likelihood estimation meta-analyses
Activation likelihood estimation approaches were implemented using the GingerALE software, 3.0.2 (Eickhoff *et al.*, 2009). In short, a 3D image is created from each foci group. The 3D image derives from the mask, individual foci and a Gaussian blur; a full width at half maximum is empirically derived from the subject size of the experiments (Eickhoff *et al.*, 2009). The three-dimensional probabilities of the activation foci are then combined for each voxel, resulting in modeled activation maps. The resulting Activation Likelihood Estimation (ALE) scores are computed by finding the convergence across all modeled activation maps, which are then compared to an empirically defined null distribution (Eickhoff *et al.*, 2012; Turkeltaub *et al.*, 2012). GingerALE 3.0.2 implements a random effects model that computes an above-chance clustering between the experiments (instead of between foci), a subject-size-related variable uncertainty and limitation of the effects of a single experiment. Talairach and Tournoux coordinates were first converted into MNI coordinates using the Lancaster transform.

Two independent coordinate-based meta-analyses on functional brain activity during mentalizing in adults and in children/adolescents were conducted. All results were thresholded at a cluster forming threshold of $P < 0.001$ (uncorrected) and a permutation-based cluster-level family-wise error (FWE) rate correction of $P < 0.05$ with 1000 permutations [standard recommendations (Eickhoff *et al.*, 2016)]. Additionally, a conjunction analysis was computed, indicating the common neural substrates activated both in adults and in children/adolescents. Conjunction analyses are based on each individual meta-analysis and a pooled dataset of all participants testing for similarity or voxel-wise minimum between the two thresholded ALE images. Contrast analyses between adults and children/adolescents were computed by repeatedly sampling 22 out of the 206 studies in adults (500 iterations, without replacement) and contrasting these to the 22 studies identified in children/adolescents. The ensuing maps were binarized and then averaged to create a probability map indicating how likely significantly higher convergence was observed in children compared to adults and vice versa. As a control measure, an additional conjunction analysis was carried out based on the iterative resampling approach described above.

To explore differences in brain activity during mentalizing in younger children compared to adolescents, we conducted individual age-categories-based follow-up meta-analyses for children (average age below 12) and adolescents (average age above 12) based on the 22 studies identified (**Supplementary Information 3**). A cut-off of 12 years on average represents both literature discussing the age of 12 as an approximate start of adolescence (Spear, 2000) and allowed roughly even powered number of experiments entering each subgroup analysis. The meta-analysis for children was based on 65 activation foci from 12 contrasts including 219 subjects; the meta-analysis on adolescents was based on 152 activation foci from 10 contrasts including 260 subjects. All images are displayed using the Mango imaging software 4.1 and the Colin27 brain template (available at http://brainmap.org/ale/). All thresholded ALE images described in this manuscript are available at https://identifiers.org/neurovault.collection:10407.

Meta-analytic connectivity modeling
Meta-analytic connectivity modeling (MACM) was used to explore functional connectivity during mentalizing in adults. MACM derives patterns of neural coactivation with studies in the Brain-Map database (Fox and Lancaster, 2002; Robinson *et al.*, 2010, 2012). Analyses were conducted for adults only since the studies included in the BrainMap database (www.brainmap.org) used for

Table 1. Functional neuroimaging studies considered in the meta-analysis on mentalizing in adults, including number of subjects (N) and task type (further details are provided in Supplementary Information 2)

First author, year	N	Task type	First author, year	N	Task type	First author, year	N	Task type
Gallagher*, 2000	6	ToM cartoon, ToM reading	Kim*, 2005	14	Matching faces with situation	Todorov*, 2007	9	Matching faces with behavior
Russell*, 2000	7	Reading the Mind in the Eyes	Ochsner*, 2005	16	Self-referential thinking (reading)	Wakusawa*, 2007	31	Irony/metaphor
Vogeley*, 2001	8	ToM reading	Aichhorn*, 2006	21	Visual perspective taking	Young*, 2007	27	False belief
Ferstl*, 2002	9	ToM reading	Elliott*, 2006	12	Reward processing	Abraham*, 2008	17	ToM reading
Martin*, 2003	12	Frith–Happé	Fukui*, 2006	16	Reward processing	Brüne*, 2008	13	ToM cartoon
Saxe*, 2003	25	False belief	Fukui*, 2006	16	Reward processing	Hooker*, 2008	20	False belief
Decety*, 2004	12	Computer/human interaction	Marjoram*, 2006	13	Humor, false belief	Kédia*, 2008	29	Pain/harm in others
Gallagher*, 2004	13	Expressive gestures	Moriguchi*, 2006	38	Frith–Happé	Kliemann*, 2008	26	False belief
German*, 2004	16	Pretended/real actions	Saxe*, 2006	12	False belief	Kobayashi*, 2008	16	False belief
Gobbini*, 2004	10	Face familiarity	Saxe*, 2006	12	False belief	Krach*, 2008	20	Prisoner's dilemma
Grèzes*, 2004	6	False belief	Spiers*, 2006	20	ToM cartoon	Malhi*, 2008	20	Frith–Happé
Leibenluft*, 2004	7	Own/others' children face processing	Uchiyama*, 2006	20	Sarcasm	Mason*, 2008	18	ToM reading
Platek*, 2004	5	Reading the Mind in the Eyes	Völlm*, 2006	13	ToM cartoon	Rilling*, 2008	20	Prisoner's dilemma
Rilling*, 2004	19	Prisoner's dilemma	Cheng*, 2007	14	Pain/harm in others	Samson*, 2008	17	Humor
Seger*, 2004	12	Food preferences of others	Gilbert*, 2007	16	Evaluation of helpfulness (reading)	Sommer*, 2008	18	Emotion attribution
Walter*, 2004	13	ToM cartoon	Gobbini*, 2007	24	Frith–Happé, false belief	Vanderwal*, 2008	17	Frith–Happé
Walter*, 2004	12	ToM cartoon	Kobayashi*, 2007	24	False belief	Young*, 2008	14	False belief
Bhatt*, 2005	16	Self-referential thinking (reading)	Mitchell, 2007	20	False belief	Aichhorn*, 2009	21	False belief
den Ouden*, 2005	11	ToM reading	Schulte-Rüther*, 2007	26	Emotional state evaluation (images)	Assaf*, 2009	19	Computer/human interaction
Harris*, 2005	12	ToM reading	Sommer*, 2007	16	False belief	Bahnemann*, 2009	25	Cartoon ToM
Jenkins*, 2009	15	False belief	Rapp*, 2010	15	Irony	Spunt*, 2011	15	Action identification (images)
Kircher*, 2009	12	Prisoner's dilemma	Ross*, 2010	15	Frith–Happé	van der Meer*, 2011	19	False belief
Krach*, 2009	24	Prisoner's dilemma	Shibata*, 2010	13	Irony	Walter*, 2011	109	ToM cartoon
Mano*, 2009	18	ToM reading	Sommer*, 2010	12	False belief	Young*, 2011	17	False belief
Otsuka*, 2009	24	ToM reading	Sommer*, 2010	14	ToM cartoon	Becchio*, 2012	16	Reach-to-grasp action movies
Sripada*, 2009	26	Computer/human interaction	Wolf*, 2010	18	ToM cartoon/movie	Canessa*, 2012	27	ToM images
Walter*, 2009	12	ToM cartoon	Yoshida*, 2010	12	Predict peer strategy during game	Chaminade*, 2012	18	Computer/human interaction
Young*, 2009	28	False belief	Young*, 2010	17	False belief	Cheung*, 2012	20	False belief
Abraham*, 2010	22	False belief	Zaitchik*, 2010	15	False belief	Das*, 2012	22	Frith–Happé
Adams*, 2010	28	Reading the Mind in the Eyes	Centelles*, 2011	14	ToM motion movie	de Achával*, 2012	14	Reading the Mind in the Eyes
Castelli*, 2010	24	Reading the Mind in the Eyes	Dodell-Feder*, 2011	62	False belief	Döhnel*, 2012	18	False belief
Focquaert*, 2010	24	Reading the Mind in the Eyes	Koelkebeck*, 2011	15	Frith–Happé	Hartwright*, 2012	19	False belief
Hooker*, 2010	15	ToM cartoon	Lee*, 2011	13	False belief	Kestemont*, 2012	34	ToM reading
Jimura*, 2010	34	False belief	Liew*, 2011	18	Interpretation of others' gestures	Mascaro*, 2012	21	Reading the Mind in the Eyes
Kim*, 2010	24	Matching faces with situation	Ma*, 2011	30	ToM reading	Mier*, 2012	13	ToM reading/faces
Lombardo*, 2010	33	ToM reading	Ma*, 2011	15	ToM reading	Moran*, 2012	128	Frith–Happé, moral judgment,

(continued)

Table 1. (Continued)

First author, year	N	Task type	First author, year	N	Task type	First author, year	N	Task type
Marsh*, 2010	24	Action identification (reading)	Mason*, 2011	10	ToM reading	Rabin*, 2012	18	Images of others'/own events
Mier*, 2010	16	ToM reading/faces	McAdams*, 2011	17	Frith–Happé	Roser*, 2012	14	False belief
Mier*, 2010	40	ToM reading/faces	Otsuka*, 2011	22	ToM reading	Spotorno*, 2012	20	Irony
Modinos*, 2010	36	ToM cartoon	Polosan*, 2011	14	Computer/human interaction	Spunt*, 2012a	21	Action identification (images)
Murphy*, 2010	10	Evaluation of others' attributes	Rothmayr*, 2011	12	False belief	Spunt*, 2012b	22	Action identification (images)
Pincus*, 2010	9	Reading the Mind in the Eyes	Schnell*, 2011	21	ToM cartoon	Uchiyama*, 2012	20	Sarcasm/metaphors
Rabin*, 2010	18	Images of others'/own events	Shibata*, 2011	15	Indirect speech	van Ackeren*, 2016	25	Indirect speech processing
Veroude*, 2012	25	False belief	Spunt*, 2014	29	Action identification (images)	Bravo*, 2017	14	Auditory ToM
Bodden*, 2013	30	False belief	Van Hoeck*, 2014	19	ToM reading	Desmet*, 2017	17	Frith–Happé
Contreras*, 2013	36	ToM reading, false belief	Alderson-Day*, 2015	19	False belief	Döhnel*, 2017	22	False belief
Corradi-Dell'Acqua*, 2013	46	False belief	Frank*, 2015	34	False belief	Eddy*, 2017	25	False belief
Dufour*, 2013	27	False belief	Hartwright*, 2015	21	False belief	Feng*, 2017	23	Indirect replies
Hervé*, 2013	42	ToM reading	Kandylaki*, 2015	20	False belief	Lewis*, 2017	17	ToM reading
Kullman*, 2013	18	Reading the Mind in the Eyes	Kanske*, 2015	25	ToM reading/faces	Massau*, 2017	50	Moral judgment of others' behavior
McAdams*, 2013	18	Frith–Happé	Littlefield*, 2015	23	ToM reading/faces	Mier*, 2017	44	ToM reading/faces
Saft*, 2013	26	ToM cartoon	Mohnke*, 2015	297	ToM cartoon	Özdem*, 2017	21	Eye gaze evaluation
Schiffer*, 2013	22	Reading the Mind in the Eyes	Ott*, 2015	20	Frith–Happé	Powell*, 2017	12	Predict peer strategy during game
van der Meer*, 2013	19	False belief	Schlaffke*, 2015	39	ToM cartoon	White*, 2017	23	Pain/harm in others
Varga*, 2013	24	Irony	Schurz*, 2015	22	Visual perspective taking	White*, 2017	23	Pain/harm in others
Ampe*, 2014	17	Action identification (images)	Spunt*, 2015	480	False belief	Ammons*, 2018	14	Frith–Happé
Dodell-Feder*, 2014	18	ToM reading	Wang*, 2015	56	ToM cartoon	Bartholomeusz*, 2018	22	ToM cartoon
Dodell-Feder*, 2014	18	False belief	Willert*, 2015	81	ToM cartoon	Bitsch*, 2018	20	Prisoner's dilemma
Feng*, 2014	17	Humor	Bardi*, 2016	22	False belief	Bliksted*, 2018	17	Frith–Happé
Hartwright*, 2014	20	False belief	Dungan*, 2016	24	False belief	Grant*, 2018	50	ToM reading
Lee*, 2014	19	False belief	Eddy*, 2016	50	False belief	Herold*, 2018	12	Irony
Mier*, 2014	18	ToM reading/faces	Hennion*, 2016	25	Frith–Happé	Lee*, 2018	16	Pain/harm in others
Reniers*, 2014	15	ToM faces	Jacoby*, 2016	20	False belief	Lin*, 2018	39	ToM reading
Riekki*, 2014	23	Frith–Happé	Kirkovski*, 2016	23	Frith–Happé	Niemi*, 2018	16	Moral judgments of others
Schneider*, 2014	16	False belief	Lavoie*, 2016	19	ToM reading	Nijhof*, 2018	21	False belief
Schuwerk*, 2014	21	False belief	Schmitgen*, 2016	21	ToM cartoon	Lassalle*, 2019	20	Pain/harm in others
Ohtsubo*, 2018	37	Others apologizing	Tsoi*, 2018	25	Pain/harm in others	Zhu*, 2019	30	Guilt/shame in others
Sommer*, 2018	15	False belief	Wurm*, 2018	18	Action identification (images)			
Specht*, 2018	18	ToM cartoon	Zhang*, 2018	58	Ambiguous ToM reading			
Thye*, 2018	18	Reading the Mind in the Eyes	Greven*, 2019	25	Body judgment of others			

* = only first authors are listed; N = number of subjects; ToM = Theory of Mind; Frith–Happé = Frith–Happé animations or adaptations thereof; ToM cartoon = comics or cartoons eliciting mentalizing; ToM reading = sentences or statements eliciting mentalizing; ToM faces = images of faces showing an intention or affective state; ToM movie = movie clips eliciting mentalizing. The full references of this table can be found in Supplementary Information 6.

Table 2. Functional neuroimaging studies considered in the meta-analysis on mentalizing in children/adolescents, including number (N) and mean age of subjects, contrast and *P* values/correction (MNI coordinates are provided in **Supplementary Information 3**). Two studies (Kobayashi *et al.*, 2008; Sommer *et al.*, 2010) reported separate coordinates for adults and children and were, therefore, considered for the meta-analysis in children/adolescents and in adults separately

First author, year	N	Age [mean age ± SD/ range in years]	Task type	Contrast	P value, correction†
Ohnishi[*a], 2004	11	[10.0/7–13]	Frith–Happé	ToM animation > control	$P < 0.05$ uc
Wang[*a], 2006	12	[11.9 ± 1.8/9–14]	Irony	Irony > control	SVC at $P < 0.05$, $k \geq 37$
Blakemore[*b], 2007	19	[14.8/12–18]	ToM reading	ToM statements > physical causality	Random fields theory corr. or SVC at $P < 0.05$
Kobayashi[*a], 2007	24	[9.1 ± 1.2/8–11]	False belief	False belief > physical causality	$P < 0.005$ uc
Moriguchi[*b], 2007	16	[13.4 ± 2.2/9–16]	Frith–Happé	ToM animation > control condition	$P < 0.001$ uc, $k \geq 50$
Pfeifer[*a], 2007	12	[10.2/9–10]	Self-referential thinking (auditory)	Self > social knowledge	$P < 0.005$ uc, $k \geq 10$
Burnett[*b], 2008	19	[14.8/11–18]	Guilt/embarrassment in others or self	Social (guilt/embarrassment) > basic emotion (disgust/fear)	SVC at $P < 0.05$
Decety[*a], 2008	17	[9.0/7–12]	Pain in others	Pain > no pain (body parts)	$P < 0.005$ uc, $k \geq 8$
Kobayashi[*a], 2008	12	[10.1 ± 1.0/8–11]	False belief	False belief > physical causality	$P < 0.005$ uc
Pfeifer[*b], 2009	12	[12.7/11–13]	Self-referential thinking (auditory)	Self > social knowledge	Corr. at $P < 0.05$
Saxe[*a], 2009	13	[8.7/6–10]	Auditory ToM	Mental state stories > physical facts	$P < 0.001$ uc, $k \geq 5$
Sommer[*a], 2010	10	[11.3 ± 0.7/10–12]	False belief	False > true belief	Cluster-level corr. or SVC at $P < 0.01$
Gweon[*a], 2012	20	[8.5/5–11]	ToM reading	ToM statements > physical causality	Monte Carlo simulation corr. at $P < 0.05$, $k \geq 200$
Schulte-Rüther[*b], 2012	21	[15.8 ± 1.9/12–18]	Frith–Happé	ToM animation > control	Voxel-level FWE corr., $k \geq 30$
Sebastian[*b], 2012	47	[14.1 ± 1.7/10–16]	False belief	Affective ToM > physical causality, Cognitive ToM > physical causality	Cluster-level FWE corr. at $P < 0.05$
Yokota[*a], 2013	28	[8.9/8–9]	ToM cartoon	Social > less social	Cluster-level FWE corr. at $P < 0.05$
O'Nions[*b], 2014	48	[13.9 ± 1.7/10–16]	False belief	Cognitive ToM > control	Peak-level FWE corr. at $P < 0.05$
Overgaauw[*b], 2014	32	[15.5/12–19]	Reading the Mind in the Eyes	Mental state > control	FDR corr. at $P < 0.05$, $k \geq 10$
White[*b], 2014	33	[13.7/11–17]	False belief	Cognitive ToM > control	FWE corr. at $P < 0.05$
Kana[*b], 2015	13	[12.7/10–15]	Frith–Happé	ToM animation > control	Monte Carlo simulation corr. at $P < 0.05$, $k \geq 100$
Alkire[*a], 2018	28	[10.4 ± 1.5/8–12]	Predict peer strategy during game	Mental state prediction > control	Cluster-level corr. at $P < 0.05$, $k \geq 86$
Mukerji[*a], 2019	32	[11.1 ± 1.4/9–12]	False belief	False belief > false photograph	$P < 0.001$ uc, $k \geq 10$ or FWE corr. at $P < 0.05$

* = only first authors are listed; N = number of participants; SD = standard deviation; ToM = Theory of Mind; † = correction is not accounted for in the resulting meta-analysis; Frith–Happé = Frith–Happé animations or adaptations; ToM cartoon = comics or cartoons eliciting mentalizing; ToM reading = sentences or statements eliciting mentalizing; uc = uncorrected; corr. = corrected; SVC = small volume correction; k = number of voxels in cluster.
[a]Studies entering the subgroup analyses in children.
[b]Studies entering the subgroup analyses in adolescents. The full references of this table can be found in Supplementary Information 6.

connectivity modeling are almost exclusively based on adult literature. Consequently, no MACM using children/adolescents was possible. Individual steps for connectivity modeling are described in **Supplementary Information 4**. In short, three analyses were conducted: (i) connectivity analyses for which all duplicates between the meta-analysis in adults and the BrainMap search findings were omitted (i.e. studies investigating mentalizing in adults that were already included in our own meta-analyses), (ii) all paradigms of the BrainMap database entered the analysis (including Theory of Mind/mentalizing tasks) and (iii) connectivity analyses for each of the nine ROIs individually based on all

paradigms in the BrainMap database were repeated to report which specific region was coactivated with any other area in the brain.

Results

Activation likelihood estimation meta-analysis results

The individual ALE meta-analysis for 206 functional neuroimaging studies of mentalizing in adults revealed nine significant clusters of activation, including bilateral temporoparietal junction
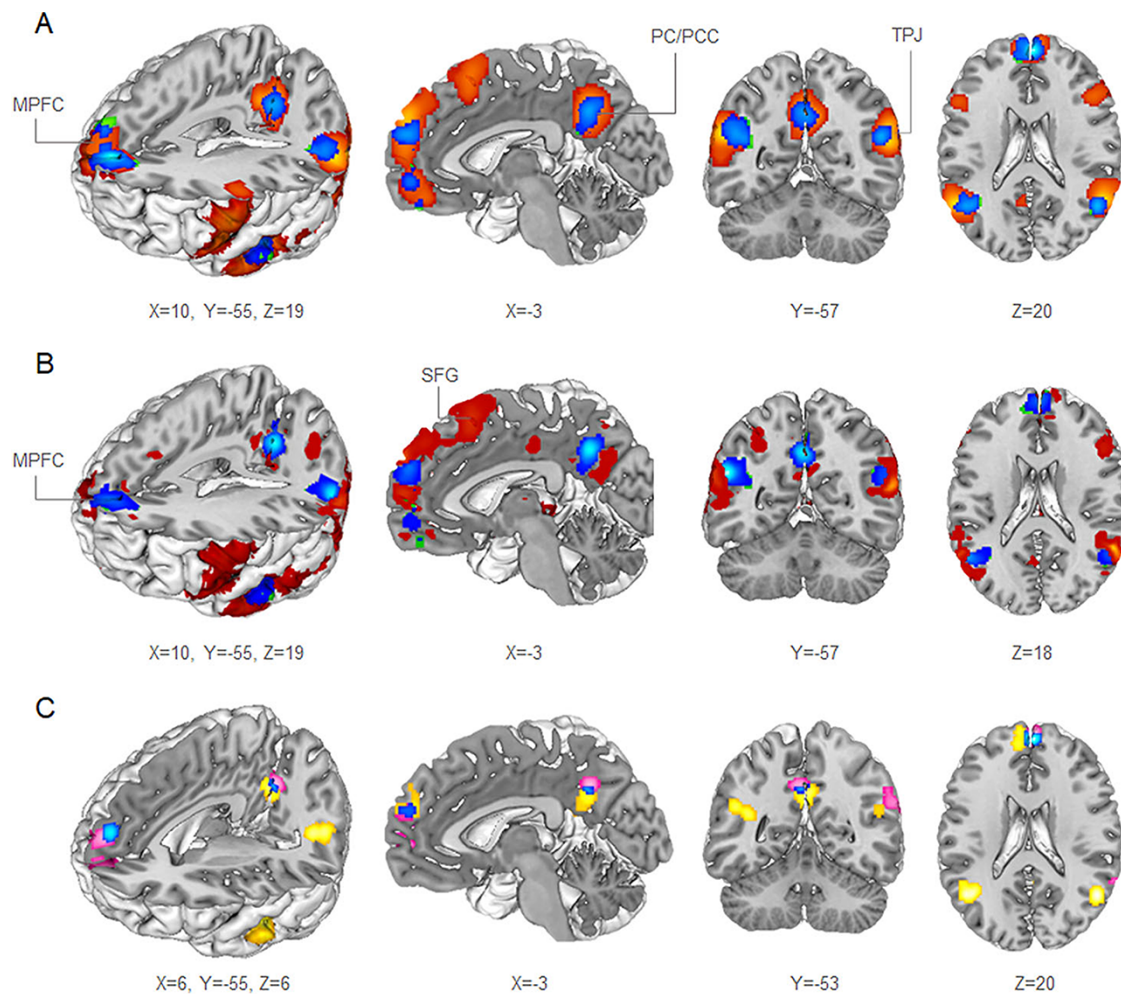
Fig. 1. Overlay of meta-analysis results for (A) adults (red) and children/adolescents (green; almost fully covered since overlapping with the conjunction results) and the conjunction analysis of both groups (blue) during mentalizing. Overlapping brain activity in adults and children/adolescents was identified for medial prefrontal cortex (MPFC), precuneus (PC)/posterior cingulate gyrus (PCC), temporoparietal junction (TPJ) and middle temporal gyri. (B) Contrast analyses for adults > children/adolescents (red) and children/adolescents > adults (green; almost fully covered since overlapping with the conjunction results) and the conjunction analysis of both groups (blue) during mentalizing. Increased activity for adults compared to children was, for example, detected in middle MPFC, superior and inferior frontal gyri (SFG/IFG) and middle temporal gyri (MTG). (C) Children (below 12 years of age; pink), adolescents (12 years and older; yellow) and the conjunction analysis of both age groups (blue). Common brain activity was detected in MPFC and PC/PCC (all P < 0.05, FWE corrected).

extending into the middle temporal gyrus, precuneus and medial and inferior/middle frontal gyri. The individual ALE meta-analysis on 22 studies in children/adolescents resulted in seven significant clusters of activation, including ventromedial and middle medial frontal cortex, bilateral temporoparietal junction, precuneus/posterior cingulate gyrus and middle/superior temporal gyri. The conjunction analysis examining the overlap of activation in studies in adults and children/adolescents resulted in seven clusters of brain activation reflecting mentalizing and included ventromedial and middle medial prefrontal cortex, precuneus, bilateral temporoparietal junction and middle/superior temporal gyri (Figure 1A and Table 3). Finally, the contrast analysis for increased activation during mentalizing for adults compared to children/adolescents, based on a robust test including resampling of the adult studies, resulted in a total of 42 clusters (18 clusters with a volume of >100 voxels) in areas including superior medial frontal cortex, bilateral superior/middle/inferior frontal gyri, posterior temporoparietal junction (including middle temporal gyri

and superior parietal lobule), posterior precuneus, thalamus, claustrum/insula and right occipital pole (Figure 1B and Table 4; full list of clusters in **Supplementary Information 7**; entire output at https://osf.io/fe5vu/). The contrast analysis for increased activation for children/adolescents compared to adults yielded eight clusters (seven clusters with a volume of >100 voxels), including ventromedial and middle medial prefrontal cortex, precuneus, bilateral temporoparietal junction and middle/superior temporal gyri (Figure 1B and Table 4; https://osf.io/fe5vu/). The added conjunction analysis based on the resampling approach yielded seven clusters that were highly similar (i.e. including the same regions) to the initial conjunction analysis (Figure 1B and Table 4; https://osf.io/fe5vu/).

To investigate potential confounds introduced by task variability, we conducted additional analyses using more restrictive criteria of including Theory of Mind tasks only (e.g. false belief tasks, Frith–Happé animations and Theory of Mind cartoon tasks). This led to comparable results (**Supplementary Information 5**). Notably, the right middle frontal gyrus previously detected in

Table 3. Meta-analytic results for studies in adults, studies in children/adolescents, and the conjunction (∩) of study findings in adults and children/adolescents

Cluster	Region	H	Vol	Weighted center x	y	z	Local maxima x	y	z	BA	ALE extrema
Adults											
1	Superior/middle temporal gyrus	L	27 048	−54	−39	6	−52	−58	24	39	0.16314
							−56	−10	−16	21	0.09503
							−56	−48	4	22	0.08342
							−58	−44	4	22	0.08245
							−54	−2	−24	21	0.08228
							−54	2	−28	21	0.08187
							−52	−34	−4	21	0.07534
							−62	−20	−10	21	0.06008
							−48	10	−36	38	0.05558
2	Superior/middle temporal gyrus	R	22 896	54	−32	2	56	−54	26	39	0.14155
							56	−54	18	39	0.13739
							54	−2	−22	21	0.11530
							60	−8	−18	21	0.10536
							50	8	−30	21	0.07466
							46	14	−32	38	0.06757
							52	−34	−2	−	0.06248
							50	−72	8	37	0.05878
3	Middle medial/superior frontal gyrus	L/R	20 704	−1	54	20	−6	56	32	8	0.12811
							0	46	−18	10	0.07336
							2	54	−12	10	0.06272
							2	44	44	8	0.04970
							4	38	38	8	0.04734
							4	42	34	6	0.04575
4	Inferior frontal gyrus	L	11 120	−48	24	3	−54	24	8	45	0.09785
							−48	28	−10	47	0.09691
							−42	10	28	9	0.05533
5	Precuneus	L	10 680	1	−55	35	−2	−54	36	31	0.15210
6	Inferior/middle frontal gyrus	R	8112	50	26	7	56	28	8	45	0.10600
							52	30	−6	45	0.07474
							48	22	22	46	0.06643
							36	24	−12	47	0.05135
7	Medial superior frontal gyrus	L/R	4992	−5	19	56	−4	18	56	6	0.07184
							−4	18	52	6	0.07093
							8	24	54	8	0.03584
8	Middle frontal gyrus	L	2344	−43	5	51	−44	6	52	6	0.06286
9	Middle frontal gyrus	R	1896	44	9	45	44	8	44	6	0.05884
Children/adolescents											
1	Medial/superior frontal gyrus	R	3224	2	56	21	4	56	20	9	0.03730
							10	56	32	8	0.01775
2	Superior/middle temporal gyrus	L	2864	−45	−58	23	−46	−58	22	39	0.02365
							−42	−58	20	22	0.02262
3	Precuneus, posterior cingulate gyrus	L	2536	−1	−54	33	0	−54	34	31	0.02384
							0	−50	24	30	0.01660
4	Middle/superior temporal gyrus	R	2008	52	8	−26	54	2	−24	21	0.02020
							52	12	−24	38	0.01934
							46	14	−32	38	0.01530
5	Superior temporal gyrus, supramarginal gyrus, inferior parietal lobule	R	1384	52	−58	21	50	−58	20	22	0.02618
							58	−52	24	40	0.01311
							54	−46	24	40	0.01189
6	Medial frontal gyrus	R	1368	2	55	−9	0	54	−8	−	0.02087
							2	50	−18	10	0.01329
7	Middle/inferior temporal gyrus	L	1200	−56	−4	−21	−56	−2	−22	21	0.02409
							−58	−14	−22	21	0.01316
Conjunction: Adults ∩ children/adolescents											
1	Medial/superior frontal gyrus	R	2912	2	56	21	4	56	20	9	0.03730
							10	56	32	8	0.01775
2	Superior/middle temporal gyrus	L	2624	−46	−58	23	−46	−58	22	39	0.02365
							−42	−58	20	22	0.02262

(continued)

Table 3. (Continued)

Cluster	Region	H	Vol	Weighted center x	y	z	Local maxima x	y	z	BA	ALE extrema
3	Precuneus, posterior cingulate gyrus	L	2448	−1	−54	34	0	−54	34	31	0.02384
							0	−50	24	30	0.01660
4	Middle/superior temporal gyrus	R	1736	52	7	−26	54	2	−24	21	0.02020
							52	12	−24	38	0.01934
							46	14	−32	38	0.01530
5	Superior temporal gyrus, supramarginal gyrus, inferior parietal lobule	R	1320	52	−57	21	50	−58	20	22	0.02618
							58	−52	24	40	0.01311
							54	−46	24	40	0.01189
6	Middle/inferior temporal gyrus	L	1128	−56	−4	−21	−56	−2	−22	21	0.02409
							−58	−14	−22	21	0.01316
7	Medial frontal gyrus	R	888	1	54	−10	0	54	−8	–	0.02087
							2	50	−18	10	0.01329

H = hemisphere; R = right; L = left; Vol = volume in mm^3; *x, y, z* coordinates are in MNI space; BA = Brodmann area (if applicable).

Table 4. Meta-analytic contrast analyses for studies in adults compared to children/adolescents. Clusters with a minimal voxel number of 100 are reported (for a full list, see Supplementary Information 7). For completeness, the conjunction analysis of the resampled adult group and children/adolescents is also provided

Cluster	Region	H	Vol	Coordinates x	y	Z
Adults > children/adolescents						
1	Medial frontal gyrus, pre-supplementary motor area	L	2132	−2	58	32
2	Temporoparietal junction, inferior parietal lobule, angular gyrus, supra-marginal gyrus	L	1925	−58	−54	22
3	Inferior parietal lobule, angular gyrus, middle temporal gyrus	R	1162	56	−52	16
4	Inferior frontal gyrus	R	919	58	32	4
5	Inferior frontal gyrus, frontal orbital cortex	L	825	−48	26	−12
6	Middle frontal gyrus	L	658	−42	8	52
7	Anterior middle temporal gyrus	R	528	58	−8	−18
8	Middle frontal gyrus	L	366	−43	5	51
9	Precuneus	R	309	4	−62	30
10	Middle frontal gyrus	R	163	40	8	38
11	Superior parietal lobule, intraparietal sulcus	L	161	−34	−54	40
12	Insula	L	156	−30	24	−6
13	Inferior lateral occipital cortex	R	155	32	−96	−10
14	Cerebellum (crus)	L	152	−28	−76	−34
15	Superior/middle frontal gyurs	L	134	−20	30	34
16	Thalamus	R	129	8	−24	−6
17	Anterior middle temporal gyrus	R	117	50	6	−38
18	Thalamus	L	116	−10	−18	2
Children/adolescents > adults						
1	Medial superior frontal gyrus	R	353	2	56	20
2	Inferior parietal lobule, angular gyrus	L	318	−42	−60	28
3	Precuneus, posterior cingulate gyrus	L/R	307	0	−50	28
4	Temporal pole, middle temporal gyrus	R	242	54	10	−22
5	Medial frontal gyrus, frontal pole	R	168	6	58	−4
6	Inferior parietal lobule, angular gyrus	R	130	48	−60	20
7	Middle/superior temporal gyrus	L	129	−56	−2	−20
Conjunction: Adults ∩ children/adolescents						
1	Medial/superior frontal gyrus	R/L	372	0	56	26
2	Inferior parietal lobule, angular gyrus	L	312	−50	−58	24
3	Precuneus, posterior cingulate gyrus	L	305	−2	−54	36
4	Middle/superior temporal gyrus	R	222	52	0	−24
5	Middle temporal gyrus	L	125	−56	−4	−20
6	Inferior parietal lobule, angular gyrus	R	120	54	−56	18
7	Medial frontal cortex	R/L	113	0	52	−12

H = Hemisphere; R = right; L = left; Vol = Volume in voxels; *x, y, z* coordinates are in MNI space.

adults and the ventromedial prefrontal cortex reported in children and the conjunction were no longer significant. However, when using more lenient statistics (a cluster forming threshold of $P < 0.001$, uncorrected), activation in both the right middle frontal gyrus (adults) and ventromedial prefrontal cortex (children, conjunction) were also visible.

Table 5. Meta-analytic findings for children (below 12 years of age), adolescents (above 12 years of age), and the conjunction analysis (∩) of studies in children below and adolescents above 12 years of age

Cluster	Region	H	Vol	Weighted center			Local maxima			BA	ALE extrema
				x	Y	z	x	y	z		
Children (below 12 years of age)											
1	Medial frontal gyrus	L	1496	3	57	19	2	56	20	9	0.02213
2	Precuneus	L	768	−3	−55	37	−2	−56	36	7	0.01623
3	Medial frontal gyrus	R	712	7	59	0	6	58	0	10	0.01264
4	Supramarginal gyrus, superior temporal gyrus	R	600	59	−52	26	60	−52	24	40	0.01214
							56	−54	32	39	0.00897
Adolescents (12 years and older)											
1	Superior/middle temporal gyrus	L	1992	−44	−57	20	−46	−58	20	22	0.02206
							−42	−58	20	22	0.02194
2	Superior/medial frontal gyrus	R/L	1976	−4	55	24	−8	54	36	8	0.01604
							4	56	20	9	0.01599
							−6	60	22	9	0.01481
							−8	52	18	9	0.01424
3	Cingulate gyrus, posterior cingulate gyrus	R	1432	1	−53	29	2	−54	32	31	0.01788
							0	−50	24	30	0.01656
4	Middle/inferior temporal gyrus	L	1088	−57	−5	−20	−58	−2	−20	21	0.01722
							−58	−14	−22	21	0.01290
5	Middle temporal gyrus	R	912	50	−60	20	50	−60	20	19	0.02386
Conjunction: Children ∩ adolescents											
1	Medial frontal gyrus	R	680	3	55	21	4	56	20	9	0.01599
2	Cingulate gyrus	L	120	−2	−54	34	0	−56	34	31	0.01167

H = hemisphere; R = right; L = left; Vol = volume in mm^3; BA = Brodmann area; x, y, z coordinates are in MNI space.

Follow-up analyses: mentalizing in younger children and adolescents

The ALE meta-analysis for children (average age below 12 years) resulted in four significant clusters of activation, including bilateral medial frontal gyri, precuneus and right temporoparietal junction. In adolescents (average age above 12 years), five significant clusters of activation were identified in middle medial prefrontal cortex, bilateral temporoparietal junction/superior temporal gyri, middle and inferior temporal gyri and cingulate gyrus extending into precuneus. The conjunction analysis of both age groups resulted in two clusters of significant common activation across both groups, including middle medial prefrontal cortex and precuneus/posterior cingulate cortex (Figure 1C and Table 5).

Meta-analytic connectivity modeling

By December 2019, the BrainMap database contained 3406 publications with 16 901 contrasts and 76 016 subjects. The BrainMap search results for each ROI are listed in Table 6. Results include paradigms for, for example, motor tasks/button press, semantic discrimination or face discrimination. The MACM analysis for all ROIs together (identical to the meta-analytic results in adults) revealed functional connectivity with bilateral middle and inferior frontal gyri extending into insula, medial superior frontal gyri, bilateral superior temporal gyri, left inferior parietal lobule extending into supramarginal gyrus, right superior parietal lobule and bilateral thalamus/basal ganglia (caudate, putamen and globus pallidus; results in Figure 2 and Table 7). The connectivity results, including all paradigms in the BrainMap database and for each ROI separately, are reported in **Supplementary Information 8 and 9**, respectively.

Discussion

This study aimed to integrate and compare functional neuroimaging reports on mentalizing in adults, children and adolescents. Across all age categories (children, adolescents and adults), activation increases during mentalizing were observed in three key regions of the social brain, namely medial prefrontal cortex, precuneus and right temporoparietal junction. Conjunction analyses in adults and children or adolescents indicated overlapping neural activity during mentalizing for both groups in medial prefrontal cortex, precuneus, bilateral temporoparietal junction and middle temporal gyri. Adults furthermore recruited regions including the bilateral inferior, middle and superior frontal gyri, superior parts of the medial frontal cortex, insula and occipital pole during mentalizing as indicated by meta-analytic contrast analyses using a robust resampling approach. When examining statistically significant differences in convergence that are higher in the studies of children and adolescents as compared to a resampled adult group, the resulting areas fully corresponded to regions that are identified through conjunction analyses (i.e. areas recruited in both age groups). Exploration of the functional connectivity network originating from the identified clusters of common activation during mentalizing in adults indicated connectivity with bilateral thalamus, basal ganglia and inferior/superior parietal lobule extending into the supramarginal gyrus. Finally, subgroup analyses comparing younger participants (<12 years) to adolescents (>12 years) revealed that both groups engage the middle medial prefrontal cortex, precuneus and right temporoparietal junction, but adolescents additionally recruit the left temporoparietal junction and middle/inferior temporal cortex during mentalizing.

Across children, adolescents and adults, consistent recruitment of medial prefrontal cortex, precuneus and temporoparietal junction was observed. Medial prefrontal cortex and tem-

Table 6. BrainMap database search results (i.e. number of foci, contrasts and subjects) for each region of interest derived from the meta-analysis in adults

Region	H	Weighted center			Foci	Contrasts	N
		x	y	z			
Superior/middle temporal gyrus (temporoparietal junction)	L	−54	−39	6	633	51	818
Superior/middle temporal gyrus (temporoparietal junction)	R	54	−32	2	771	38	593
Middle medial frontal gyrus	L/R	−1	54	20	372	32	466
Inferior frontal gyrus	L	−48	24	3	681	41	526
Precuneus	L	1	−55	35	483	42	708
Inferior/middle frontal gyrus	R	50	26	7	561	34	555
Medial superior frontal gyrus	L/R	−5	19	56	757	52	802
Middle frontal gyrus	L	−43	5	51	809	47	683
Middle frontal gyrus	R	44	9	45	684	37	527

H = hemisphere; R = right; L = left; N = number of subjects.

poroparietal junction are commonly associated with mentalizing (Van Overwalle, 2009; Mar, 2011; Schurz *et al.*, 2014; van Veluw and Chance, 2014; Molenberghs *et al.*, 2016). The medial prefrontal cortex has been suggested to play a generic role when reasoning about one's own or others' mental states (Amodio and Frith, 2006; Moll and de Oliveira-Souza, 2007; Blakemore, 2008; Shamay-Tsoory *et al.*, 2009; Molenberghs *et al.*, 2016). The ventromedial prefrontal cortex is more strongly related to social emotion processing or regulation of emotions (Hiser and Koenigs, 2018). The temporoparietal junction is prominently recruited using false belief or perspective-taking tasks (Decety and Lamm, 2007) and has been suggested to comprise a subregion selective for reasoning about others' mental states (Saxe and Kanwisher, 2003; Van Overwalle, 2009). Tasks involving the reorientation of attention and representing a sense of agency have likewise shown to lead to activation increases in temporoparietal regions (Decety and Lamm, 2007). Finally, the precuneus has been suggested to play a significant role in memory and mental imagery needed to construct different perspectives (Cavanna and Trimble, 2006; Schurz *et al.*, 2013). Overall, brain regions showing activation during mentalizing across development have been broadly linked to the reorientation of attention, memory processes and mental imagery. Such patterns of neural engagement may indicate that the neural basis supporting mentalizing is somewhat stable from a young age on, possibly reflecting an early specialization of parts of the social brain (Bowman *et al.*, 2019). Our findings are supported by behavioral evidence of mentalizing skills starting to develop early in life and continuing until young adulthood (Meins *et al.*, 2002; Blakemore, 2008; Knudsen and Liszkowski, 2012).

Here, bilateral inferior, middle and superior frontal gyri, medial sections of the superior frontal gyri, insula and occipital pole were identified in adults only but not in children and adolescents as indicated by contrast analyses. This is in line with the involvement of inferior and middle frontal gyri in late-developing higher-order cognitive functions, including attentional processes (Japee *et al.*, 2015), working memory (Leung *et al.*, 2002), response inhibition (Swick *et al.*, 2008; Hampshire *et al.*, 2010), semantic processing (Costafreda *et al.*, 2006) and observation of movements via the mirror neuron system (Kilner *et al.*, 2009). The medial superior frontal cortices are similarly involved in higher cognitive processing, including memory and executive functions (Boisgueheneuc *et al.*, 2006; Nachev *et al.*, 2008; Li *et al.*, 2013) or higher-order emotion processes (Seitz *et al.*, 2008; Rochas *et al.*, 2013). The insula and occipital pole have been related to mentalization processes as, for example, trait judgments of familiar others (Laurita *et al.*, 2017), social emotion regulation (Grecucci *et al.*, 2013) or spontaneous mentalizing (Spiers and Maguire, 2006). Our findings may be indicative of specializations within the social brain network across age and are in line with data indicating a late development of higher cognitive functions (Gogtay *et al.*, 2004; Tamnes *et al.*, 2010; Simmonds *et al.*, 2017). Regions with increased activation for children/adolescents compared to adults almost fully overlapped with areas observed in the conjunction analysis, encompassing bilateral temporoparietal junction, medial prefrontal cortex and precuneus. The observed difference may be due to the repeated resampling of adult studies while keeping the 22 studies in children constant. Additionally, differences may result from a differing threshold selection, as studies in children/adolescents tend to be more lenient.

Our follow-up subgroup analyses investigating younger children (<12 years) and adolescents (>12 years) revealed that children up to 12 years of age commonly engage brain areas within the middle medial prefrontal cortex, precuneus and right temporoparietal junction, while adolescents commonly activate a more adult-like set of brain regions, including medial prefrontal cortex, precuneus, bilateral temporoparietal junction
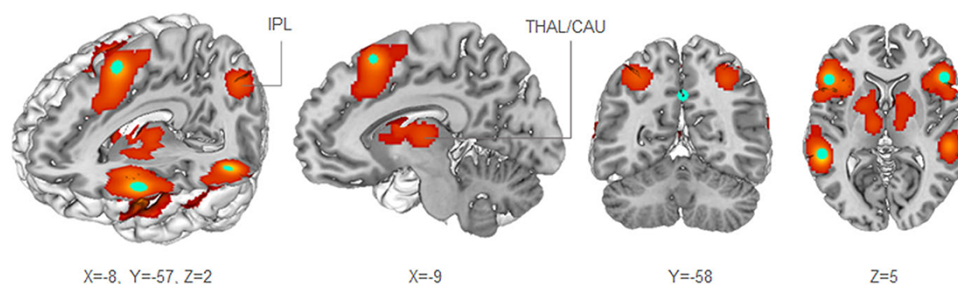

Fig. 2. Meta-analytic connectivity modeling results for adults. Regions of interest identified in our meta-analysis (mint) and resulting clusters of functional connectivity (red), including inferior parietal lobule (IPL) and thalamus/caudate (THAL/CAU). Coordinates are in MNI space.

Table 7. Peak activation report from meta-analytic connectivity modeling for studies in adults

Cluster	Region[a]	H	Vol	Weighted center			Local maxima			BA	ALE extrema
				x	y	z	x	y	z		
1	Middle/inferior frontal gyrus	L	39 648	−45	16	20	−44	4	50	6	0.26320
							−48	26	2	45	0.21631
							−46	18	22	9	0.15168
2	Inferior/middle frontal gyrus, insula	R	28 752	46	18	16	50	26	8	45	0.19116
							44	10	46	6	0.15275
							38	22	−6	–	0.13327
							46	18	−4	13	0.10349
							52	22	28	9	0.08854
							48	12	26	9	0.08448
							48	34	24	9	0.05953
							46	38	24	9	0.05867
3	Medial superior frontal gyrus	L	20 424	0	18	48	−4	18	54	6	0.26774
4	Middle/superior temporal gyrus	L	10 968	−56	−37	5	−54	−40	6	22	0.26631
							−58	−6	−6	22	0.07007
5	Inferior parietal lobule, supramarginal gyrus	L	9656	−35	−52	46	−32	−52	48	40	0.11232
							−46	−38	42	40	0.07748
6	Superior temporal gyrus	R	7032	56	−32	2	54	−32	2	22	0.18224
							62	−16	0	22	0.05018
							62	−40	14	22	0.04970
							56	−46	10	22	0.04956
							58	−6	−2	22	0.04817
7	Thalamus, caudate, globus pallidus	L	5568	−13	−4	7	−10	−14	6	–	0.08201
							−12	2	14	–	0.07733
							−18	2	6	–	0.06834
8	Globus pallidus, caudate, putamen, thalamus	R	4736	16	−1	7	14	2	0	–	0.06502
							14	8	8	–	0.06335
							20	2	8	–	0.06294
							12	−14	8	–	0.06068
9	Superior parietal lobule	R	4504	34	−55	49	34	−54	48	7	0.09201
							28	−64	56	7	0.07454

H = Hemisphere; R = right; L = left; Vol = Volume in mm³; x, y, z coordinates are in MNI space; BA = Brodmann area (if applicable).
[a]Co-activation with 5 mm spheres around bilateral superior/middle temporal gyri (−54 −39 6, 54–32 2), medial middle (−1 54 20), medial superior (−5 19 56), middle (−43 5 51, 44 9 45) and inferior frontal gyri (−48 24 3, 50 26 7) and precuneus (1–55 35).

and anterior middle/inferior temporal cortices (Van Overwalle, 2009; Mar, 2011; Schurz *et al.*, 2014; van Veluw and Chance, 2014; Molenberghs *et al.*, 2016). In the present meta-analyses, development of the temporoparietal junction is indicated by unilateral (i.e. right-hemispheric) activation in children but bilateral activation in adolescents. Notably, interpretation is limited by the small number of studies and by the cross-sectional designs included. Thus, the present results may broadly point toward developmental effects based on categorical observations only (Blakemore, 2008, 2012b). Brain maturation, especially of prefrontal brain regions, is paralleled by increasing mentalizing skills and cognitive development across age (Blakemore *et al.*, 2007a; Blakemore, 2008, 2012a,b; Crone and Dahl, 2012), while the development of temporoparietal junction is suggested to underlie an increasing selectivity for mental state processing (Saxe *et al.*, 2009; Gweon *et al.*, 2012). In adults, functional connectivity between areas of the social brain network (i.e. bilateral superior/middle temporal gyri, precuneus, medial superior frontal gyri and bilateral middle and inferior frontal gyri) and further connectivity to bilateral thalamus, basal ganglia and inferior and superior parietal lobule was observed. The rostral section of the inferior parietal lobule [Brodmann Area 40 (Brodmann, 1909)] and the superior parietal lobule are located dorsally of the temporoparietal junction. The inferior parietal lobule forms part of the mirror neuron system and is involved in the imitation of actions needed to adapt to social situations and when processing

semantic and affective information (Iacoboni, 2009; Molenberghs *et al.*, 2009; Caspers *et al.*, 2010), whereas the superior parietal lobule is implicated in working memory and visuospatial attention (Corbetta *et al.*, 1995; Koenigs *et al.*, 2009). The thalamus and basal ganglia (e.g. striatum, composed by the caudate nucleus and putamen) are implicated in reward-based learning and higher-level behavioral control and regulation (e.g. DeLong and Wichmann, 2009). Connectivity between the thalamus/basal ganglia and the cerebral cortex (e.g. dorsolateral prefrontal cortex and anterior cingulate cortex) has been commonly reported in emotion processing and higher-order cognitive processes such as mentalizing (Postuma and Dagher, 2006; Di Martino *et al.*, 2008; Molenberghs *et al.*, 2016). Inclusion of Theory of Mind tasks in the paradigms entering the connectivity analyses led to an additional coactivation cluster in the middle medial prefrontal cortex, which may indicate that this area is specifically activated during mentalizing (Schurz *et al.*, 2014; Molenberghs *et al.*, 2016). For developmental populations, only few studies so far have examined functional connectivity during mentalizing. Burnett and Blakemore (2009) reported increased functional connectivity between the ventromedial prefrontal cortex and left temporoparietal junction/posterior superior temporal sulcus in adolescents compared to adults, possibly reflecting increasing specialization of the network connections during skill development. Similarly, Richardson *et al.* (2018) detected increased connectivity with age between temporoparietal junction, precuneus

and medial prefrontal cortex in children aged 3–12 years during an implicit Theory of Mind task. Others reported no age effects in connectivity during mentalizing but stable connectivity patterns between associated areas (e.g. medial prefrontal cortex and temporoparietal junction and precuneus) and striatum/dorsolateral prefrontal cortex [(McCormick *et al.*, 2018) in 8–16 year olds] or within mentalizing regions [temporoparietal junction, superior temporal sulcus and precuneus (Mukerji *et al.*, 2019) in 9–13 year olds]. Such differences in findings may arise due to variations in the tasks employed or the characteristics of the group studied.

Limitations and future steps

Using a meta-analytic approach increases statistical power, which is especially useful for developmental neuroscience research, where studies are often characterized by small sample sizes. However, meta-analytic approaches also entail shortcomings, and the present findings depend on the quality and methodological approaches of the publications included. Such variability was partly addressed by conducting a meta-analysis with more restrictive definitions for Theory of Mind tasks, yielding comparable results. While the activity in two regions was no longer significant, these clusters emerged when using more lenient statistics, indicating possible power issues. Moreover, it is to note that the meta-analysis in adults comprised more studies than the meta-analysis in children and adolescents. Overall, the meta-analysis in adults is better powered and, therefore, more likely to have captured a true effect, while the meta-analysis in children and adolescents may have to be interpreted with more caution. The search for studies in children/adolescents was furthermore conducted later than the one for adults, which may have benefitted the number of studies entering the meta-analysis in children/adolescents. However, evidence in adults was large ($N = 5286$) and an inclusion of a few more studies was considered unlikely to change this. This is supported by the comparability of the present findings in adults and past meta-analytic work (Molenberghs *et al.*, 2016). The interpretation of the meta-analytic output obtained here is, based on its methodology, limited to the location of the neural activation clusters, whereas cluster size or strength of activation of each age group cannot be interpreted (Eickhoff *et al.*, 2009). Furthermore, this method cannot account for differences in the initial thresholding of the studies included, although such variation may influence the coordinates entering the analyses and thus the outcome of the present meta-analyses. Moreover, the contrast and conjunction analyses may show an overlap of regions, which is a consequence of the approach implemented (repeated resampling). While the direct comparison of children and adolescents is of interest, these analyses are based on average ages within groups without consideration of age ranges and, therefore, need to be interpreted with caution. During adolescence, many different variables individually or interactively influence development, which cannot be accounted for here. The present work may only inform about age categories and does not directly inform about continuing development, for which longitudinal studies were required (Blakemore, 2008; Blakemore *et al.*, 2010; Luna *et al.*, 2010). Finally, meta-analyses are subject to publication biases and may propagate these [e.g. due to the inclusion of positive/significant findings while ignoring null results (Klapwijk *et al.*, 2019)].

To advance the field of mentalizing, future longitudinal measurements of brain activity during development are needed. These may allow drawing generalizable conclusions about fine-grained linear and nonlinear maturational trajectories associated with complex cognitive functions, as, for example, reported for the frontal cortex (Ordaz *et al.*, 2013; Qu *et al.*, 2015; Simmonds *et al.*, 2017). Longitudinal designs may further characterize the neural correlates of mentalizing during major transitional steps [e.g. the transition from kindergarten to formal school education (Blair, 2002; Blair and Raver, 2015)]. Open science frameworks and data sharing options (see, e.g. https://osf.io, https://aspredicted.org or https://neurovault.org) may be considered by all researchers to provide options for data replication and compilation (Kliemann and Adolphs, 2018; Klapwijk *et al.*, 2019).

Conclusion

Our meta-analyses shed further light on the neural basis of mentalizing in adults, children and adolescents. While adults and children/adolescents show similar brain activation patterns during mentalizing in areas such as the middle medial prefrontal cortex, precuneus and temporoparietal junction, the adult brain recruits further brain regions, including medial and lateral prefrontal cortices. This may be due to the development of more complex cognitive processes. Our results indicate that essential neural components for mentalizing are at least partially established in childhood, reflecting a likely early stability and specialization of parts of the social brain network. Future studies using longitudinal designs may further clarify the precise underlying mechanisms of neural continuity and change during mentalizing from childhood to adolescence and adulthood.

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Conflict of interest

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Supplementary data

Supplementary data are available at *SCAN* online.

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