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 (Björnvinsson 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., 2003). 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; Schwerk 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 (Gween 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; Overgaard 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 (Overgaard et al., 2015). Overgaard 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 (Gween 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 other reports decrease 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; Gween 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; Madhyaastha 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; Molenaerghs 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 hyoactivations 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.

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 enough power of 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 BrainMap 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
| First author, year | N | Task type | First author, year | N | Task type | First author, year | N | Task type | First author, year | N | Task type |
|-------------------|---|-----------|-------------------|---|-----------|-------------------|---|-----------|-------------------|---|-----------|
| Gallagher*, 2000  | 6 | Task type | Gallagher*, 2000  | 6 | Task type | Gallagher*, 2000  | 6 | Task type | Gallagher*, 2000  | 6 | Task type |
| Russiell*, 2000  | 9 | Task type | Russiell*, 2000  | 9 | Task type | Russiell*, 2000  | 9 | Task type | Russiell*, 2000  | 9 | Task type |
| Voges*, 2000  | 15 | Task type | Voges*, 2000  | 15 | Task type | Voges*, 2000  | 15 | Task type | Voges*, 2000  | 15 | Task type |
| Ferri*, 2000  | 18 | Task type | Ferri*, 2000  | 18 | Task type | Ferri*, 2000  | 18 | Task type | Ferri*, 2000  | 18 | Task type |
| Frith*, 2000  | 16 | Task type | Frith*, 2000  | 16 | Task type | Frith*, 2000  | 16 | Task type | Frith*, 2000  | 16 | Task type |
| Perrett*, 2000  | 17 | Task type | Perrett*, 2000  | 17 | Task type | Perrett*, 2000  | 17 | Task type | Perrett*, 2000  | 17 | Task type |
| Perrett*, 2000  | 18 | Task type | Perrett*, 2000  | 18 | Task type | Perrett*, 2000  | 18 | Task type | Perrett*, 2000  | 18 | Task type |
| Perrett*, 2000  | 19 | Task type | Perrett*, 2000  | 19 | Task type | Perrett*, 2000  | 19 | Task type | Perrett*, 2000  | 19 | Task type |
| Perrett*, 2000  | 20 | Task type | Perrett*, 2000  | 20 | Task type | Perrett*, 2000  | 20 | Task type | Perrett*, 2000  | 20 | Task type |
| Perrett*, 2000  | 21 | Task type | Perrett*, 2000  | 21 | Task type | Perrett*, 2000  | 21 | Task type | Perrett*, 2000  | 21 | Task type |
| Perrett*, 2000  | 22 | Task type | Perrett*, 2000  | 22 | Task type | Perrett*, 2000  | 22 | Task type | Perrett*, 2000  | 22 | Task type |
| Perrett*, 2000  | 23 | Task type | Perrett*, 2000  | 23 | Task type | Perrett*, 2000  | 23 | Task type | Perrett*, 2000  | 23 | Task type |
| Perrett*, 2000  | 24 | Task type | Perrett*, 2000  | 24 | Task type | Perrett*, 2000  | 24 | Task type | Perrett*, 2000  | 24 | Task type |
| Perrett*, 2000  | 25 | Task type | Perrett*, 2000  | 25 | Task type | Perrett*, 2000  | 25 | Task type | Perrett*, 2000  | 25 | Task type |
| Perrett*, 2000  | 26 | Task type | Perrett*, 2000  | 26 | Task type | Perrett*, 2000  | 26 | Task type | Perrett*, 2000  | 26 | Task type |
| Perrett*, 2000  | 27 | Task type | Perrett*, 2000  | 27 | Task type | Perrett*, 2000  | 27 | Task type | Perrett*, 2000  | 27 | Task type |
| Perrett*, 2000  | 28 | Task type | Perrett*, 2000  | 28 | Task type | Perrett*, 2000  | 28 | Task type | Perrett*, 2000  | 28 | Task type |
| Perrett*, 2000  | 29 | Task type | Perrett*, 2000  | 29 | Task type | Perrett*, 2000  | 29 | Task type | Perrett*, 2000  | 29 | Task type |
| Perrett*, 2000  | 30 | Task type | Perrett*, 2000  | 30 | Task type | Perrett*, 2000  | 30 | Task type | Perrett*, 2000  | 30 | Task type |
| Perrett*, 2000  | 31 | Task type | Perrett*, 2000  | 31 | Task type | Perrett*, 2000  | 31 | Task type | Perrett*, 2000  | 31 | Task type |
| Perrett*, 2000  | 32 | Task type | Perrett*, 2000  | 32 | Task type | Perrett*, 2000  | 32 | Task type | Perrett*, 2000  | 32 | Task type |
| Perrett*, 2000  | 33 | Task type | Perrett*, 2000  | 33 | Task type | Perrett*, 2000  | 33 | Task type | Perrett*, 2000  | 33 | Task type |
| Perrett*, 2000  | 34 | Task type | Perrett*, 2000  | 34 | Task type | Perrett*, 2000  | 34 | Task type | Perrett*, 2000  | 34 | Task type |
| Perrett*, 2000  | 35 | Task type | Perrett*, 2000  | 35 | Task type | Perrett*, 2000  | 35 | Task type | Perrett*, 2000  | 35 | Task type |
| Perrett*, 2000  | 36 | Task type | Perrett*, 2000  | 36 | Task type | Perrett*, 2000  | 36 | Task type | Perrett*, 2000  | 36 | Task type |
| Perrett*, 2000  | 37 | Task type | Perrett*, 2000  | 37 | Task type | Perrett*, 2000  | 37 | Task type | Perrett*, 2000  | 37 | Task type |
| Perrett*, 2000  | 38 | Task type | Perrett*, 2000  | 38 | Task type | Perrett*, 2000  | 38 | Task type | Perrett*, 2000  | 38 | Task type |
| Perrett*, 2000  | 39 | Task type | Perrett*, 2000  | 39 | Task type | Perrett*, 2000  | 39 | Task type | Perrett*, 2000  | 39 | Task type |
| Perrett*, 2000  | 40 | Task type | Perrett*, 2000  | 40 | Task type | Perrett*, 2000  | 40 | Task type | Perrett*, 2000  | 40 | Task type |
| Perrett*, 2000  | 41 | Task type | Perrett*, 2000  | 41 | Task type | Perrett*, 2000  | 41 | Task type | Perrett*, 2000  | 41 | Task type |
| Perrett*, 2000  | 42 | Task type | Perrett*, 2000  | 42 | Task type | Perrett*, 2000  | 42 | Task type | Perrett*, 2000  | 42 | Task type |
| Perrett*, 2000  | 43 | Task type | Perrett*, 2000  | 43 | Task type | Perrett*, 2000  | 43 | Task type | Perrett*, 2000  | 43 | Task type |
| Perrett*, 2000  | 44 | Task type | Perrett*, 2000  | 44 | Task type | Perrett*, 2000  | 44 | Task type | Perrett*, 2000  | 44 | Task type |
| Perrett*, 2000  | 45 | Task type | Perrett*, 2000  | 45 | Task type | Perrett*, 2000  | 45 | Task type | Perrett*, 2000  | 45 | Task type |
| Perrett*, 2000  | 46 | Task type | Perrett*, 2000  | 46 | Task type | Perrett*, 2000  | 46 | Task type | Perrett*, 2000  | 46 | Task type |
| Perrett*, 2000  | 47 | Task type | Perrett*, 2000  | 47 | Task type | Perrett*, 2000  | 47 | Task type | Perrett*, 2000  | 47 | Task type |
| Perrett*, 2000  | 48 | Task type | Perrett*, 2000  | 48 | Task type | Perrett*, 2000  | 48 | Task type | Perrett*, 2000  | 48 | Task type |
| Perrett*, 2000  | 49 | Task type | Perrett*, 2000  | 49 | Task type | Perrett*, 2000  | 49 | Task type | Perrett*, 2000  | 49 | Task type |
| Perrett*, 2000  | 50 | Task type | Perrett*, 2000  | 50 | Task type | Perrett*, 2000  | 50 | Task type | Perrett*, 2000  | 50 | Task type |

Note: (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| False belief |
| 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 | 21| Action identification (images) |
| Prince*, 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 |
| Vemude*, 2012      | 25| False belief | Spunt*, 2014 | 29| Action identification (images) | van Ackeren*, 2016 | 25| Indirect speech processing |
| Bodden*, 2013      | 30| False belief | Van Hoeck*, 2014 | 19| ToM reading | Bravo*, 2017 | 14| Auditory ToM |
| Contrenas*, 2013   | 36| ToM reading, false belief | Alderson-Day*, 2015 | 19| False belief | Desmet*, 2017 | 17| Frith–Happé |
| Corradi-Dell’Acqua* | 46| False belief | Frank*, 2015 | 34| False belief | Döhnel*, 2017 | 22| False belief |
| Dufour*, 2013      | 27| False belief | Hartwright*, 2015 | 21| False belief | Eddy*, 2017 | 25| False belief |
| Hervé*, 2013       | 42| ToM reading | Kandyaki*, 2015 | 20| False belief | Feng*, 2017 | 23| Indirect replies |
| Kullman*, 2013      | 18| Reading the Mind in the Eyes | Kanske*, 2015 | 25| ToM reading/faces | Lewis*, 2017 | 17| ToM reading |
| McAdams*, 2013     | 18| Frith–Happé | Littlefield*, 2015 | 23| ToM reading/faces | Massau*, 2017 | 50| Moral judgment of others’ behavior |
| Saff*, 2013        | 26| ToM cartoon | Mohme*, 2015 | 297| ToM cartoon | Mier*, 2017 | 44| ToM reading/faces |
| Schiffer*, 2013    | 22| Reading the Mind in the Eyes | Ott*, 2015 | 20| Frith–Happé | Ozdem*, 2017 | 21| Eye gaze evaluation game |
| van der Meer*, 2013 | 19| False belief | Schafke*, 2015 | 39| ToM reading | Powell*, 2017 | 12| Predict peer strategy during game |
| 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 | White*, 2017 | 23| Pain/harm in others |
| Dodell-Feder*, 2014 | 18| ToM reading | Wang*, 2015 | 56| ToM cartoon | Ammons*, 2018 | 14| Frith–Happé |
| Dodell-Feder*, 2014 | 18| False belief | Willert*, 2015 | 81| ToM cartoon | Bartholomeusz*, 2018 | 22| ToM cartoon |
| Dufour*, 2014      | 17| Humor | Bardi*, 2016 | 22| False belief | Bitsch*, 2018 | 20| Prisoner’s dilemma |
| Hartwright*, 2014  | 20| False belief | Dungan*, 2016 | 24| False belief | Blästedt*, 2018 | 17| Frith–Happé |
| Lee*, 2014         | 19| False belief | Eddy*, 2016 | 50| False belief | Grant*, 2018 | 50| ToM reading |
| Mier*, 2014        | 18| ToM reading/faces | Hemion*, 2016 | 25| Frith–Happé | Herold*, 2018 | 12| Irony |
| Reniers*, 2014     | 15| ToM faces | Jacoby*, 2016 | 20| False belief | Lee*, 2018 | 16| Pain/harm in others |
| Riekkö*, 2014      | 23| Frith–Happé | Korkoski*, 2016 | 23| Frith–Happé | Lin*, 2018 | 39| ToM reading |
| Schneider*, 2014   | 16| False belief | Lavoie*, 2016 | 19| ToM reading | Niemi*, 2018 | 16| Moral judgments of others |
| Schwerck*, 2014    | 21| False belief | Schmitgen*, 2016 | 21| ToM cartoon | Nijhof*, 2018 | 21| False belief |
| Ohtsubo*, 2018     | 37| Others apologizing | Tsui*, 2018 | 25| Pain/harm in others | Lassalle*, 2019 | 20| Pain/harm in others |
| Sommer*, 2018     | 18| False belief | Wurm*, 2018 | 18| Action identification (images) | Zhu*, 2019 | 30| Guilt/shame in others |
| Specht*, 2018      | 18| ToM cartoon | Zhang*, 2018 | 58| Ambiguous ToM reading | |
| Thye*, 2018        | 18| Reading the Mind in the Eyes | Greven*, 2015 | 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.
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
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 gyr. 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 adults and the ventromedial prefrontal cortex reported in children/adolescents, bilateral temporoparietal junction and middle/superior temporal cortex during mentalizing (Frith, 2006) were also visible.

### 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 gyr, 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 16901 contrasts and 76016 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 gyr, 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 gyr. 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 temporoparietal 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, 2009; 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
| Cluster | Region | H   | Vol  | x     | y     | z     | Weighted center | BA | ALE extrema |
|---------|--------|-----|------|-------|-------|-------|-----------------|----|-------------|
| Adults  | Superior/middle temporal gyrus | L   | 27048| −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     |
|         | Superior/middle temporal gyrus | R   | 22896| 54 32 | 2     |       | 56 −54 26      | 39 | 0.14555     |
|         |        |     |      |       |       |       | 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     |
|         | Middle medial/superior frontal gyrus | L/R | 20704| −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     |
|         | Inferior frontal gyrus | L   | 11120| −48 24| 3     |       | −54 24         | 8  | 0.09785     |
|         |        |     |      |       |       |       | −48 28 −10     | 47 | 0.09691     |
|         |        |     |      |       |       |       | −42 10 28      | 9  | 0.05533     |
|         | Precuneus | L   | 10680| −55 35|       |       | −2 −54 36      | 31 | 0.15210     |
|         | 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     |
|         | 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  | 0.05854     |
|         | Middle frontal gyrus | L   | 2344 | −43 5 | 51    |       | −44 6 52       | 6  | 0.06286     |
|         |        |     |      |       |       |       | 44 8 44        | 6  | 0.05884     |
|         | Middle frontal gyrus | R   | 1896 | 44 9 | 45    |       | 44 8 44        | 6  | 0.05884     |
| Children/adolescents | Medial/superior frontal gyrus | R   | 3224 | 2 56 | 21    |       | 4 56 20        | 9  | 0.03730     |
|         |        |     |      |       |       |       | 10 56 32       | 8  | 0.01775     |
|         | Superior/middle temporal gyrus | L   | 2864 | −45 −58 23| | −46 −58 22 39| | 0.02365 | |
|         |        |     |      |       |       |       | −42 −58 20     | 22 | 0.02262     |
|         | Precuneus, posterior cingulate gyrus | L   | 2536 | −1 −54 33| | 0 −54 34 31| | 0.02384 | |
|         |        |     |      |       |       |       | 0 −50 24       | 30 | 0.01660     |
|         | 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     |
|         | 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     |
|         | Medial frontal gyrus | R   | 1368 | 2 55 −9| | 0 54 −8| | 0.02087 | |
|         |        |     |      |       |       |       | 2 50 −18       | 10 | 0.01329     |
|         | Middle/inferior temporal gyrus | L   | 1200 | −56 −4 −21| | −56 −2 −22 21| | 0.02409 | |
|         |        |     |      |       |       |       | −58 −14 −22    | 21 | 0.01316     |
| Conjunction: Adults \(\cap\) children/adolescents | Medial/superior frontal gyrus | R   | 2912 | 2 56 | 21    |       | 4 56 20        | 9  | 0.03730     |
|         |        |     |      |       |       |       | 10 56 32       | 8  | 0.01775     |
|         | Superior/middle temporal gyrus | L   | 2624 | −46 −58 23| | −46 −58 22 39| | 0.02365 | |
|         |        |     |      |       |       |       | −42 −58 20     | 22 | 0.02262     | (continued)
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 gyrus. (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).

Table 3. (Continued)

| Cluster | Region                                                      | H  | Vol  | x     | y     | z     | BA | ALE extrema |
|---------|-------------------------------------------------------------|----|------|-------|-------|-------|----|-------------|
| 3       | Precuneus, posterior cingulate gyrus                        | L  | 2448 | -1    | -54   | 34    |    |             |
| 4       | Middle/superior temporal gyrus                              | R  | 1736 | 52    | 7     | -26   |    |             |
| 5       | Superior temporal gyrus, supramarginal gyrus, inferior parietal lobule | R  | 1320 | 52    | -57   | 21    |    |             |
| 6       | Middle/inferior temporal gyrus                              | L  | 1128 | -56   | -4    | -21   |    |             |
| 7       | Medial frontal gyrus                                        | R  | 888  | 1     | 54    | -10   |    |             |

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

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;
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 | x   | y   | z   |
|---------|--------|---|-----|-----|-----|-----|
| Adults > children/adolescents | Medial frontal gyrus, pre-supplementary motor area | L | 2132 | −2  | 58  | 32  |
|         | Temporoparietal junction, inferior parietal lobule, angular gyrus, supra-marginal gyrus | L | 1925 | −58 | −54 | 22  |
|         | Inferior parietal lobule, angular gyrus, middle temporal gyrus | R | 1162 | 56  | −52 | 16  |
|         | Inferior frontal gyrus | R | 919  | 58  | 32  | 4   |
|         | Inferior frontal gyrus, frontal orbital cortex | L | 825  | −48 | 26  | −12 |
|         | Middle frontal gyrus | L | 658  | −42 | 8   | 52  |
|         | Anterior middle temporal gyrus | R | 528  | 58  | −8  | −18 |
|         | Middle frontal gyrus | L | 366  | −43 | 5   | 51  |
|         | Precuneus | R | 309  | 4   | −62 | 30  |
|         | Middle frontal gyrus | R | 163  | 40  | 8   | 38  |
|         | Superior parietal lobule, intraparietal sulcus | L | 161  | −34 | −54 | 40  |
|         | Insula | L | 156  | −30 | 24  | −6  |
|         | Inferior lateral occipital cortex | L | 129  | 50  | 6   | −38 |
|         | Superior/middle frontal gyurs | L | 116  | −10 | −18 | 2   |
| Children/adolescents > adults | Medial superior frontal gyrus | R | 353  | 2   | 56  | 20  |
|         | Inferior parietal lobule, angular gyrus | L | 318  | −42 | −60 | 28  |
|         | Precuneus, posterior cingulate gyrus | L/R | 307  | 0   | −50 | 28  |
|         | Temporal pole, middle temporal gyrus | R | 242  | 54  | 10  | −22 |
|         | Medial frontal gyrus, frontal pole | R | 168  | 6   | 58  | −4  |
|         | Inferior parietal lobule, angular gyrus | R | 130  | 48  | −60 | 20  |
|         | Middle/superior temporal gyrus | L | 129  | −56 | −2  | −20 |

Conjunction: Adults ∩ children/adolescents

| Cluster | Region | H/L | Vol | x   | y   | z   |
|---------|--------|-----|-----|-----|-----|-----|
| 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.

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.

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.
Children (below 12 years of age) and adolescents (above 12 years of age) 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 and right temporoparietal junction. 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 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 used in studies involving children.

### 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 | x | y | z | P | cluster region | x | y | z |
|---------|--------|---|-----|---|---|---|---|----------------|---|---|---|
| Children (below 12 years of age) | Medial frontal gyrus | L | 1946 | 3 | 57 | 19 | 2 | 56 | 20 | 9 | 0.02213 |
| Adolescents (12 years and older) | Superior/middle temporal gyrus | L | 1992 | −4 | −57 | 20 | −46 | −58 | 20 | 22 | 0.02206 |
| | Superior/middle frontal gyrus | R | 712 | −3 | −55 | 37 | −2 | −56 | 36 | 7 | 0.01623 |
| | Medial frontal gyrus | L | 600 | 59 | −52 | 26 | 60 | −52 | 24 | 40 | 0.01214 |

| Conjunction: Children ∩ adolescents | Cluster | Region | H | Vol | x | y | z | P | cluster region | x | y | z |
|----------------------------------|--------|--------|---|-----|---|---|---|---|----------------|---|---|---|
| Children (below 12 years of age) | Medial frontal gyrus | L | 1496 | 3 | 57 | 19 | 2 | 56 | 20 | 9 | 0.02213 |
| Adolescents (12 years and older) | Superior/middle temporal gyrus | L | 1992 | −4 | −57 | 20 | −46 | −58 | 20 | 22 | 0.02206 |
| | Superior/middle frontal gyrus | R | 712 | −3 | −55 | 37 | −2 | −56 | 36 | 7 | 0.01623 |
| | Medial frontal gyrus | L | 600 | 59 | −52 | 26 | 60 | −52 | 24 | 40 | 0.01214 |

### 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 | x | y | z | Foci | Contrasts | N |
|--------|---|---|---|---|------|----------|---|
| 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 |
| Superior/middle frontal gyrus | L/R | −1 | 54 | 20 | 372 | 32 | 466 |
| Inferior frontal gyrus | L | −58 | −5 | −20 | 681 | 41 | 526 |
| Inferior/middle frontal gyrus | L | −48 | 24 | 3 | 483 | 42 | 708 |
| Medial superior frontal gyrus | L/R | 50 | 26 | 7 | 563 | 34 | 555 |
| 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; Vol = volume in mm³; BA = Brodmann area; x, y, z coordinates are in MNI space.

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(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 (Boisguesheuen 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.

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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**

The authors declared that they had no conflict of interest with respect to their authorship or the publication of this article.

**Supplementary data**

Supplementary data are available at SCAN online.

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