

## REVIEW ARTICLE

# Overlapping and specific neural correlates for empathizing, affective mentalizing, and cognitive mentalizing: A coordinate-based meta-analytic study

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## Abstract

While the discussion on the foundations of social understanding mainly revolves around the notions of empathy, affective mentalizing, and cognitive mentalizing, their degree of overlap versus specificity is still unclear. We took a meta-analytic approach to unveil the neural bases of cognitive mentalizing, affective mentalizing, and empathy, both in healthy individuals and pathological conditions characterized by social deficits such as schizophrenia and autism. We observed partially overlapping networks for cognitive and affective mentalizing in the medial prefrontal, posterior cingulate, and lateral temporal cortex, while empathy mainly engaged fronto-insular, somatosensory, and anterior cingulate cortex. Adjacent process-specific regions in the posterior lateral temporal, ventrolateral, and dorsomedial prefrontal cortex might underpin a transition from abstract representations of cognitive mental states detached from sensory facets to emotionally-charged representations of affective mental states. Altered mentalizing-related activity involved distinct sectors of the posterior lateral temporal cortex in schizophrenia and autism, while only the latter group displayed abnormal empathy related activity in the amygdala. These data might inform the design of rehabilitative treatments for social cognitive deficits.

## KEYWORDS

activation likelihood estimation, affective mentalizing, autism, cognitive mentalizing, empathy, mentalizing, meta-analysis, schizophrenia, theory of mind

## 1 | INTRODUCTION

Interpersonal behaviors are a core component of humans' life (Henry, von Hippel, Molenberghs, Lee, & Sachdev, 2016), mediated by the ability to represent others' intentions, thoughts, and emotions (Arioli, Crespi, & Canessa, 2018). Over the last two decades, the growing evidence on the neuro-cognitive bases of social understanding (Fortier, Besnard, & Allain, 2018) paralleled an increasing awareness of the inconsistent theoretical, neurobiological, and semantic definitions and

classifications of the underlying processes (Cerniglia et al., 2019; Schurz et al., 2020). While this field revolves around the notions of Empathy and Theory of Mind (ToM, or mentalizing) (Dvash & Shamay-Tsoory, 2014), different terms are often used to describe similar processes and, sometimes, similar terms are used to refer to different processes (see Happe, Cook, & Bird, 2017).

The mentalizing system is generally considered to involve two distinct components, drawing inferences on others' beliefs and intentions (i.e., cognitive mentalizing) and on their emotions and feelings

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(affective mentalizing; Shamay-Tsoory, Harari, Aharon-Peretz, & Levkovitz, 2010), respectively. It is still debated, however, whether this distinction reflects in specific versus common neural bases (Molenberghs, Johnson, Henry, & Mattingley, 2016). Here, we took advantage of a meta-analytic approach to integrate—within a unitary discussion—the available fMRI evidence on the neural bases of cognitive mentalizing, affective mentalizing, and empathy, both in healthy individuals and in distinct pathological conditions, such as schizophrenia (SC) and autism, that have been strongly characterized by marked deficits in social understanding. Despite the central role of these processes in social cognition, to the best of our knowledge this is the first study addressing (a) their common versus specific neural bases in healthy individuals, and (b) possible differences in the neural bases of their altered processing across distinct pathological conditions, which are considered exemplary of social cognitive impairments.

### 1.1 | Empathy

Despite different views on its core components, it is largely acknowledged that *empathy* refers to grasping and sharing others' emotional and sensory feelings, including pain (Wu et al., 2019) compassion (Mercadillo, Diaz, Pasaye, & Barrios, 2011), embarrassment (Krach et al., 2011), and exclusion (Beeney, Franklin Jr., Levy, & Adams Jr., 2011), which however are perceived as distinct from one's own ones (Bzdok et al., 2012). According to the perception-action model of empathy (Preston & de Waal, 2017), emotional sharing and understanding entail an automatic simulation of others' experiences (Oliver, Vieira, Neufeld, Dziobek, & Mitchell, 2018), promoting prosocial behavior (Betti & Aglioti, 2016). This process relies on the fronto-insular (Fallon, Roberts, & Stancak, 2020) and anterior cingulate (ACC) cortex (Bernhardt & Singer, 2012; for a meta-analysis see Timmers et al., 2018). Some studies, however, reported only insula activation as fundamental for empathic processing (e.g., Grice-Jackson, Critchley, Banissy, & Ward, 2017). Empathy processing is often associated with the recruitment of further regions, such as pre- and postcentral gyri, inferior parietal lobule (IPL), thalamus, and amygdala (Del Casale et al., 2017), but with limited agreement on the role of these regions in empathic resonance (e.g., Gu et al., 2012).

### 1.2 | Affective and cognitive mentalizing

The automatic sharing of others' experiences differentiates empathy from mentalizing, the latter referring to representing another's mental states, such as thoughts, desires, behavioral dispositions, and even affective mental states, in terms of abstract inferences (Bzdok et al., 2012). Grasping the content of other persons' minds is key to recognize that their knowledge is different from ours, to try to explain and predict their actions, and eventually to influence their behavior by manipulating their beliefs (Baker, Jara-Ettinger, Saxe, & Tenenbaum, 2017). The core ToM network includes the medial prefrontal cortex (mPFC), precuneus, and temporoparietal junction (TPJ);

Schurz, Radua, Aichhorn, Richlan, & Perner, 2014), but other regions are recruited when mentalizing, probably depending on contingent features of experimental paradigms (e.g., Arioli, Gianelli, et al., 2020; Lin et al., 2018; Spunt & Adolphs, 2014).

Much of the debate on the neural bases of mentalizing revolves around the putative distinction between its affective and cognitive sub-components (Molenberghs et al., 2016), referring to the ability to make inferences about others' emotional versus cognitive mental states, respectively (e.g., Schlaffke et al., 2015; Sebastian et al., 2012). Cognitive mentalizing thus refers to the ability to make inferences about beliefs and motivations, while affective mentalizing refers to the ability to infer what a person is feeling (Sebastian et al., 2012). To empirically differentiate performance on cognitive versus affective mentalizing, researchers have developed several tasks, such as, for example, the Yoni task (Shamay-Tsoory & Aharon-Peretz, 2007) and the Story-based Empathy task (SET; Dodich et al., 2015). These tasks represent sensitive tools for detecting different dimensions of mentalizing impairment, across different clinical conditions, supporting the existence of two different mentalizing components (i.e., cognitive and affective mentalizing; Cerami et al., 2014; Dodich et al., 2016; Rossetto et al., 2018). Alongside the common involvement of the precuneus and TPJ bilaterally (Sebastian et al., 2012), there is meta-analytic evidence of specific activations for cognitive mentalizing in the right TPJ and superior temporal sulcus, and for affective mentalizing in the left orbitofrontal cortex, pars opercularis of the inferior frontal gyrus (IFG), and ventral premotor cortex (vPMC; Molenberghs et al., 2016). Other studies, however, reported other regions as specifically associated with affective mentalizing, for example, basal ganglia (Bodden et al., 2013), posterior cingulate cortex (Schlaffke et al., 2015), and ventromedial prefrontal cortex (vmPFC; Sebastian et al., 2012). Interestingly, the aforementioned social tasks successfully differentiate between cognitive and affective mentalizing in individuals with lesions affecting circumscribed regions thought to be related to those abilities (Shamay-Tsoory & Aharon-Peretz, 2007).

### 1.3 | Mentalizing and empathy

Empathy represents a mirroring of the emotional response that is, living “as if the same feelings or perceptions occurred to me,” on the other hand, mentalizing involves a cognitive evaluation of the others' internal state, such as thoughts and intentions for cognitive mentalizing, and emotional feelings for affective mentalizing (Cerniglia et al., 2019). Cognitive mentalizing involves inferences on other's cognitive mental states, whereas affective mentalizing involves a cognitive understanding of another person's emotional perspective, and empathy includes appropriating and sharing these feelings, at least on a gross and more automatic level (Dvash & Shamay-Tsoory, 2014). Although both affective mentalizing and empathy involves emotional state understanding, there is evidences (e.g., Gallant et al., 2020; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009) showing the distinction between these two processes.

To date, only a few studies have addressed the possible relationship between empathy, affective and cognitive mentalizing. While

lesion-based evidence suggested that affective mentalizing requires cognitive mentalizing and empathy (Shamay-Tsoory et al., 2009, 2010), this proposal has never been tested. Shamay-Tsoory et al. (2010) suggests that affective mentalizing builds on the independent contribution of the cognitive mentalizing and of the empathic processing outputs. Based on this model, a deficit in empathy or cognitive mentalizing should also be reflected in a deficit in affective mentalizing, which depends on the other two components. Psychopathic patients, with a deficit in empathy and affective mentalization, present a clinical picture that supports this model (Shamay-Tsoory et al., 2010).

An influential neuro-cognitive model suggests that empathy is associated with fronto-insular cortex, ACC, and amygdala, while cognitive mentalizing recruits the medial prefrontal cortex, STS, and TPJ, with affective mentalizing specifically engaging the vmPFC (Dvash & Shamay-Tsoory, 2014). To date, single studies have only contrasted two (out of three) such constructs, for example, affective versus cognitive mentalizing (Schlaffke et al., 2015) or empathy versus mentalizing (without distinguishing between affective and cognitive ToM; Vollm et al., 2006). Therefore, the degree of overlap versus segregation of their neural bases remains largely under-investigated (e.g., Chen & Hong, 2018). By adopting a hierarchical approach, Schurz et al. (2020) have shown the existence of three distinct clusters (cognitive, affective, and intermediate) underlying social cognitive processing. While these three clusters might underpin cognitive mentalizing, empathy, and affective mentalizing, respectively, this hypothesis requires empirical support. Interestingly, the intermediate cluster combines cognitive and affective processes, as proposed by the Shamay-Tsoory et al.'s (2010) model. These findings suggest that areas linked to the cognitive and affective clusters are functionally segregated in many task contexts, however, during intermediate tasks, cognitive and affective processes operate conjointly to support the intermediate process (Schurz et al., 2020).

An inherent limitation of this literature is represented by the confusing and inconsistent definitions of the features and functions of mentalizing and empathy systems. For instance, it has been suggested that even empathy might comprise affective and cognitive sub-components, with a putative “affective empathy” system supporting the sharing or simulation of others' affective experiences, and a “cognitive empathy” system associated with the abstract understanding of others' mental states (Schurz et al., 2020). However, the latter might be considered to overlap with the notion of *mentalizing* per se (Dvash & Shamay-Tsoory, 2014), and more specifically with *affective mentalizing* (Henry et al., 2016). Moreover, another crucial distinction has been proposed between personal distress (i.e., affect arising in response to others' suffering) and empathic care (i.e., responding to others' distress with warmth and care) (Ashar, Andrews-Hanna, Dimidjian, & Wager, 2017). Whether emotional responses that are primarily self-oriented, such as personal distress, can be considered truly empathic responses is, however, matter of debate (Henry et al., 2016).

In the light of these inconsistencies, in this work the term *empathy* will be only referred to its affective component.

## 1.4 | Empathy and mentalizing impairments in SC and autism

Mentalizing and empathy play a crucial role in social cognition, moral reasoning, and prosocial behavior (Bzdok et al., 2012; Majdandzic, Amashafer, Hummer, Windischberger, & Lamm, 2016), and thus in mental health and wellbeing (Henry et al., 2016). Autism spectrum disorder (ASD) and SC share social communication impairments paralleling defective mentalizing and empathic abilities (Tordjman, Celume, Denis, Motillon, & Keromnes, 2019), alongside defective communication, and social interaction, particularly involving reduced facial expression or body language, poor eye contact, and abnormal emotional expression (Henry et al., 2016; Tordjman et al., 2019).

In the last edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5), SC is the only condition associated with a mentalizing impairment, which additionally correlates with the severity of functional outcomes (Fett et al., 2011). Distinct tasks have highlighted mentalizing impairments in SC, such as those requiring to represent others' cognitive and emotional mental states (Russell et al., 2000; Stanford, Messinger, Malaspina, & Corcoran, 2011), and to identify social gaffes (FauxPas) (Hooker, Bruce, Lincoln, Fisher, & Vinogradov, 2011). Patients' impaired performance in these tasks has been related to a decreased activity in the superior temporal gyrus and TPJ (Adamczyk et al., 2017; Lee, Horan, Wynn, & Green, 2016). Although less investigated than mentalizing, also empathy processing might be impaired in SC, particularly concerning emotion recognition (Habel et al., 2010), affective responsiveness (Derntl, Seidel, Schneider, & Habel, 2012), and altered neural responses to others' affective cues (Harvey, Zaki, Lee, Ochsner, & Green, 2013; Singh et al., 2015).

Conversely, altered empathic responses and maladaptive emotional reactions have been often reported as core deficits in ASD (Peterson, 2014), although not unanimously (Bernhardt et al., 2014). ASD patients' decreased activity in response to emotional expressions in core regions of the social brain, such as the fusiform gyrus and the amygdala (Zalla & Sperduti, 2013), have been suggested to relate to the avoidance of eye contact (Kliemann, Dziobek, Hatri, Baudewig, & Heekeren, 2012). This proposal fits with the evidence of altered connectivity between the amygdala and fusiform face area (FFA) in ASD (e.g., Radua, Via, Catani, & Mataix-Cols, 2011), tracking the severity of social impairment (Kleinmans et al., 2008). Mentalizing seems also to be impaired in adults with ASD (Velikonja, Fett, & Velthorst, 2019). Abnormal TPJ activity has been reported in autistic patients (Schütz et al., 2020) in association with intention attribution (e.g., Schütz et al., 2020) and both implicit and explicit false belief reasoning (Nijhof, Bardi, Brass, & Wiersema, 2018).

The role played by empathy and mentalizing in social communication, and their frequent association with social anxiety (Spain, Sin, Linder, MacMahon, & Happe, 2018), explain why a thorough characterization of these constructs, their borders and relationships, as well as their neural correlates in SC and autism, is critical for designing treatments and assessing their effectiveness (Tordjman et al., 2019). For example, if cognitive mentalizing is a prerequisite for

affective mentalizing (Shamay-Tsoory et al., 2010), assessing the former ability might be needed to evaluate the specificity of an impairment in the latter. It is noteworthy, then, that none of the available meta-analyses on the neural bases of social cognitive deficits in autism distinguished between mentalizing and empathy. Furthermore, unveiling the neural bases of empathy or mentalizing in pathological conditions might help refining neurocognitive models of these crucial building blocks of social cognition.

## 1.5 | Aim of the present study

The evidence reviewed above about empathy and mentalizing highlights several gaps concerning their common versus specific neural bases. While Dvash and Shamay-Tsoory's (2014) model provides a theoretical framework for their mutual relationships, empirical evidence is needed to support, reject, or refine its main tenets. Here we addressed this issue with distinct coordinate-based meta-analyses of neuroimaging studies on empathy and both affective and cognitive mentalizing in healthy individuals. We then extended this investigation to SC and autism to assess (a) whether altered social understanding in these disorders involves regions belonging to the construct-specific networks observed in healthy individuals; (b) whether the neural bases of altered social cognitive abilities provides additional cues into their mutual relationships. For instance, based on Shamay-Tsoory et al.'s model (Shamay-Tsoory et al., 2009, 2010), defective empathy or cognitive mentalizing should be expected to entail impaired affective mentalizing.

We predicted to observe at least partially specific brain activations for the three subcomponents of social understanding under investigation: (a) a cognitive component, engaged when mentalizing requires abstract inference on others' cognitive mental states; (b) an emotional empathy component, underpinning shared neural representations of others' emotional, motor, or somatosensory experiences; (c) an intermediate process of affective mentalizing, whereby others' affective mental states are coded in terms of abstract inferences in addition to internal simulations (Schurz et al., 2020). Based on previous studies, we expected a prominent role of the dorsal and anterior/ventral TPJ sector in, respectively, cognitive mentalizing and affective mentalizing (Schurz et al., 2014). We expected also a specific role of the dorsomedial prefrontal cortex (dmPFC) in the cognitive proper aspects of mentalizing, on the other hand, when the mentalizing process involves emotional cues, we expected a vmPFC activation (Sebastian et al., 2012). The anterior-middle cingulate cortex (extending caudally into the supplementary motor area [SMA]) and the insula (extending into the IFG) are the key nodes of the interoceptive awareness system, and they might underlie the neural representation of both one's own and others' emotional states (Berntson & Khalsa, 2021), thus we expected this specific activation pattern for empathy tasks. Based on previous integrative reviews of social cognitive impairments in these disorders (Henry et al., 2016), we additionally expected to observe prominent alterations of brain activity associated with mentalizing and empathy in SC and autism,

respectively. In particular, we expected an abnormal activation in the middle temporal gyrus (MTG) and TPJ during mentalizing task in schizophrenic patients, as previously reported in other meta-analysis addressing social understanding in this patients (Kronbichler et al., 2017; Vucurovic, Caillies, & Kaladjian, 2020). Considering the literature on social brain dysfunctionality in individuals with autism spectrum, we expected abnormalities in the amygdala activation during empathic processing (Peng et al., 2020). Based on Shamay-Tsoory et al.'s model (Shamay-Tsoory et al., 2009, 2010), however, ASD patients' empathic deficit is expected to also affect the ability to understand other's affective mental states (i.e., affective mentalizing). In fact, this model predicts that a deficit in empathy is also followed by an abnormality in the affective mentalizing skills (see Section 1.3; Shamay-Tsoory et al., 2010).

## 2 | MATERIALS AND METHODS

### 2.1 | Rationale of the meta-analytic approach

We aimed to identify the brain regions *consistently* associated with the affective and cognitive facets of mentalizing (Molenberghs et al., 2016), over and beyond the contribution of neural mechanisms of empathic processing (Timmers et al., 2018). Based on previous evidence of selective social cognitive impairments in SC (Horan & Green, 2019) and autism (Sucksmith, Allison, Baron-Cohen, Chakrabarti, & Hoekstra, 2013), we additionally addressed the neural correlates of impaired mentalizing and empathic processing in these two clinical populations.

This goal was pursued with ALE, a coordinate-based metaanalytic approach using coordinates of peak locations to summarize and integrate published findings (Turkeltaub, Eden, Jones, & Zeffiro, 2002). Such as approach allows to overcome the typical limitations inherent in single neuroimaging studies, for example, sensitivity to experimental and analytic procedures, lack of replication studies, as well as small sample size (Carp, 2012). These constraints are known to increase the likelihood of false negatives (Button et al., 2013), thus pushing researchers toward procedures which, conversely, might promote false positives (Eklund, Nichols, & Knutsson, 2016; Muller et al., 2018).

First, we ran four separate ALE analyses addressing the neural processing of mentalizing (not considering sub-components), cognitive mentalizing, affective mentalizing and empathic processing in healthy individuals. Conjunction and contrast analyses allowed to unveil both common and specific activations across: (1) cognitive and affective mentalizing, (2) mentalizing and empathic processing, (3) cognitive mentalizing and empathic processing, and (4) affective mentalizing and empathic processing. Finally, we ran four additional ALE analyses comparing the neural bases of mentalizing or empathic processing across healthy controls (HCs) and either schizophrenic or autistic patients.

We aimed to investigate brain activations related to mentalizing and empathy regardless of the input sensory modality (i.e., visual or

auditory), the stimulus type (i.e., photos, videos, verbal materials, sounds, etc.), and task (e.g., comprehension, attention, etc.). All the inclusion criteria for each dataset were selected by the first author, and then checked by the other authors. This procedure, entailing a double check by independent investigators, was aimed to reduce the chances of a selection bias (Muller et al., 2018).

## 2.2 | Literature search and study selection

### 2.2.1 | Neural bases of mentalizing

We started our survey of the relevant literature by searching for “ToM fMRI” and “mentalizing fMRI” on Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed/>). After duplicate removal, a preliminary pool of 1,092 studies was first screened by title, and then by abstract. We retained only those studies fulfilling the following selection criteria (see Figure S1 for details on the procedure for study selection):

1. studies written in English language;
2. empirical fMRI studies, while excluding review and meta-analysis studies and those employing other techniques, to ensure comparable spatial and temporal resolution;
3. studies reporting whole-brain activation coordinates, rather than regions of interest (ROIs) or results of small volume correction (SVC). Studies based on ROIs or SVC should be excluded because a prerequisite for fMRI meta-analyses is that convergence across experiments is tested against a nullhypothesis of random spatial associations across the entire brain, under the assumption that each voxel has the same a priori chance of being activated (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Muller et al., 2018);
4. studies including drug-free and nonclinical participants, to prevent possible differences in brain activity associated with pharmacological manipulations or neuro-psychiatric diseases other than those under investigation;
5. studies with adult subjects (age range: 18–60 years);
6. studies requiring the understanding of others' beliefs, emotional states, and intentions, while excluding those aimed to induce an affective sharing and brain activity interpreted in terms of empathic resonance;
7. studies requiring participants to represent others' mental states by adopting an intentional stance toward others, that is, by understanding their thoughts, emotional states, desires, intentions, and future actions in terms of abstract inferences detached from a sensory stimulation. Namely, we selected contrasts that were specifically aimed to elicit brain activations interpreted by the authors in terms of “mentalizing or theory of mind network” associated with the representation or attribution of mental states, that is: a) inferences on mental states or intentions > inferences on physic or perceptual aspects, or on literal meanings other than mental states; b) attribution of emotional mental states > gender inferences (based on Baron-Cohen, Wheelwright, Hill, Raste, and Plumb's (2001) “Reading the mind in the eyes” task); c) human interactions > computer interactions, during interactive games.

Within the studies fulfilling these criteria, we retained only the contrasts between conditions differing in terms of the requirement to represent mental states.

Starting from an initial screening of 1,092 titles and abstracts, 622 papers deemed as potentially relevant were fully reviewed based on the aforementioned selection criteria (see Figure S1). We thus excluded: 134 review or meta-analysis articles; 43 studies employing techniques other than fMRI; 30 studies using ROIs or SVC; 2 studies explicitly focused on empathic processing; 41 studies focused on children or aging populations; 33 studies not reporting all the required information; 189 studies focused on clinical populations and 45 studies that did not focus on mentalizing.

We included studies fulfilling the above criteria regardless of: (a) sensory modality (e.g., visual or auditory); (b) experimental paradigm (e.g., comprehension or attentional tasks); (c) stimulus type (e.g., videos, photos, and verbal materials). Our aim was indeed to pool across different experimental paradigms to ensure both generalizability and consistency of results, within the requirement of mentalizing inherent in our research question (Radua & Mataix-Cols, 2012). This selection phase resulted in 105 studies fulfilling our criteria.

We then expanded our search for other potentially relevant studies by carefully examining both the studies quoting, and those quoted by, each of these papers, alongside previously published meta-analyses on the neural bases of mentalizing (Bzdok et al., 2012; Molenberghs et al., 2016; Spreng, Mar, & Kim, 2009; van Veluw and Chance, 2014). This second phase highlighted seven further studies fitting our search criteria. Overall, this procedure led to include in the ALE meta-analysis 112 previously published studies (see Table S1), resulting from 113 experiments (individual comparisons reported) with 2,295 subjects and 1,696 activation foci. Tasks were classified as “affective” if they required participants to infer emotional mental states, and “cognitive” if they involved understanding beliefs, intentions or goals. In total, 412 activation foci from 26 experiments were ascribed to affective mentalizing, and 1,272 activation foci from 93 experiments to cognitive mentalizing (see Table S1).

### 2.2.2 | Neural bases of empathy

We started our survey of the relevant literature by searching for “empathy fMRI” and “empathic fMRI” on Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed/>) (see Figure S2). After duplicate removal, a preliminary pool of 721 studies was first screened by title, and then by abstract. While the methodological selection criteria were the same as above (1–5), here we selected only studies reporting brain activations interpreted by the authors as related to empathic processing. To this purpose, we selected only:

6. studies aimed to elicit an affective sharing and brain activity interpreted by the authors in terms of empathic resonance, rather than mentalizing (i.e., representation, and attribution of mental states);
7. studies aimed to elicit the isomorphic experience of another's affective state. Put differently, in these studies participants were supposed to know and “feel into” another's experience. These



studies employed mostly visual, and to a lesser extent auditory or textual, stimuli conveying emotional situations which participants attended passively, or evaluated on various dimensions, without a direct involvement. Namely, we selected studies requiring participants to attend to another person's emotional state, and performing contrasts aimed to elicit brain activations interpreted by the authors in terms of empathic processing, that is: a) direct comparison between emotional stimuli and baseline/control stimuli (e.g., pain > no pain or emotion > neutral in others); b) direct comparison between an empathy task and a control task (e.g., brain activations highlighted by the contrast between rating and counting painful stimuli); c) correlation with trait empathy as measured by self-report questionnaires (e.g., Baron-Cohen and Wheelwright's (2004) Empathy Quotient (EQ)); d) correlation with valence rating (e.g., pain or unpleasantness ratings); e) observing other's exclusion, compared with inclusion, during interactive games (e.g., cyberball game; Williams, Cheung, & Choi, 2000).

Within the studies fulfilling these criteria, we retained only the contrasts between conditions differing in terms of the requirement to share another's emotional state. Thus, while mentalizing task required to develop an abstract representation of characters' (affective and cognitive) mental states, only in empathy task participants were supposed to "feel into" another's feelings (emotions, pain, compassion, etc.).

Starting from an initial screening of 721 titles and abstracts, 631 papers deemed as potentially relevant were fully reviewed based on the aforementioned selection criteria (see Figure S2). We thus excluded: 57 review or meta-analysis articles; 33 studies employing techniques other than fMRI; 11 studies using ROIs or SVC; 6 studies explicitly focused on mentalizing; 51 studies focused on children or aging populations; 28 studies not reporting all the required information; 204 studies focused on clinical populations and 161 studies that did not focus on empathic processing.

We included studies fulfilling the above criteria regardless of: (a) sensory modality (e.g., visual or auditory), (b) experimental paradigm (e.g., comprehension or attentional tasks), and (c) stimulus type (e.g., videos, photos, and verbal materials). Our aim was indeed to pool across different experimental paradigms to ensure both generalizability and consistency of results, within the requirement of an empathic processing inherent in our research question (Radua & Mataix-Cols, 2012). This selection phase resulted in 80 studies fulfilling our criteria.

We then expanded our search for other potentially relevant studies by carefully examining both the studies quoting, and those quoted by, each of these papers, alongside previously published meta-analyses on the neural bases of empathic processing (Del Casale et al., 2017; Gu et al., 2012; Lamm, Decety, & Singer, 2011; Timmers et al., 2018; Wu et al., 2019). This second phase highlighted 10 further studies fitting our search criteria. Overall, this procedure led to include in the ALE meta-analysis 90 previously published studies (see Table S2), resulting from 90 experiments (individual comparisons reported) with 2,230 subjects and 1,355 activation foci.

### 2.2.3 | Neural bases of mentalizing in SC patients versus HCs

We started our survey of the relevant literature by searching for studies on SC patients in our database of 1,092 studies on the neural bases of mentalizing (see Section 2.2.1). This search, resulting in 19 studies, was extended by carefully examining the studies included in a recent meta-analysis on the neural bases of social cognition in SC (Vucurovic et al., 2020; see Figure S3), which highlighted other 28 relevant studies. After duplicate removal, the preliminary pool of 39 studies was first screened by title and then by abstract. While the methodological selection criteria were the same as above (1–3), here we selected only studies reporting stronger brain activations, interpreted by the authors as related to mentalizing, in HCs compared with schizophrenic patients. To this purpose, we selected only:

4. studies reporting significantly different brain activation across HCs and schizophrenic patients (HC > SC). In all the selected studies SC patients had been diagnosed using the Structured Clinical Interview for the Diagnostic (SCID), and/or following the clinical criteria reported in the DSM-IV or DSM-IV-TR and/or in the Statistical Classification of Disease and Related Health Problems (ICD-10);

5. studies investigating brain activity related to representing another's mental states (as described in Section 2.2.1). Namely, we selected contrasts aimed to elicit brain activations interpreted in terms of a "mentalizing or theory of mind network" underpinning the representation or attribution of mental states.

Starting from an initial screening of 39 titles and abstracts, 24 papers deemed as potentially relevant were fully reviewed based on the aforementioned selection criteria (see Figure S3). We thus excluded: 1 study employing techniques other than fMRI; 2 studies using ROIs or SVC and 6 studies explicitly focused on empathic processing.

We included studies fulfilling the above criteria regardless of: (a) sensory modality (e.g., visual or auditory), (b) experimental paradigm (e.g., comprehension or attentional tasks), and (c) stimulus type (e.g., videos, photos, or verbal materials). Our aim was indeed to pool across different experimental paradigms to ensure both generalizability and consistency of results, within the requirement of mentalizing in HCs compared with schizophrenic patients inherent in our research question (Radua & Mataix-Cols, 2012). This selection phase resulted in 15 studies fulfilling our criteria.

We then expanded our search for other potentially relevant studies by carefully examining both the studies quoting, and those quoted by, each of these papers. This second phase highlighted four further studies fitting our search criteria. Overall, this procedure led to include in the ALE meta-analysis 19 previously published studies (see Table S3), resulting from 19 experiments (individual comparisons reported), with 305 HCs compared to 292 schizophrenic patients (SC), and 145 activation foci.

### 2.2.4 | Neural bases of empathy in SC patients versus HCs

We started our survey of the relevant literature by searching for studies on SC patients in our database of 721 studies on the neural bases

of empathy (see Section 2.2.2). This search, resulting in 15 studies, was extended by carefully examining the studies included in a recent meta-analysis on the neural bases of social cognition in SC (Vucurovic et al., 2020; see Figure S4), which highlighted other 28 relevant studies. After duplicate removal, this preliminary pool of 35 studies was first screened by title, and then by abstract. While the methodological selection criteria were the same as in Section 2.2.3 (1-4), here we selected only studies reporting stronger brain activations, interpreted by the authors as related to empathy, in HCs compared with schizophrenic patients. To this purpose, we selected only:

5. studies investigating brain activity related to the isomorphic experience of another's affective state (as described in Section 2.2.2). Namely, we selected studies requiring participants to attend to another person's emotional state, and performing contrasts aimed to elicit brain activations interpreted in terms of empathic processing.

Starting from an initial screening of 35 titles and abstracts, 27 papers deemed as potentially relevant were fully reviewed based on the aforementioned selection criteria (see Figure S4). We thus excluded: 5 studies employing techniques other than fMRI; 13 studies addressing processes other than empathy and 1 study explicitly focused on mentalizing.

We included studies fulfilling the above criteria regardless of: (a) sensory modality (e.g., visual or auditory), (b) experimental paradigm (e.g., comprehension or self-other tasks), and (c) stimulus type (e.g., videos, photos, or verbal materials). Our aim was indeed to pool across different experimental paradigms to ensure both generalizability and consistency of results, within the requirement of empathy in HCs compared with schizophrenic patients inherent in our research question (Radua & Mataix-Cols, 2012). This selection phase resulted in eight studies fulfilling our criteria.

We then expanded our search for other potentially relevant studies by carefully examining both the studies quoting, and those quoted by, each of these papers. This second phase highlighted nine further studies fitting our search criteria. Overall, this procedure led to include in the ALE meta-analysis 17 previously published studies (see Table S4), resulting from 17 experiments (individual comparisons reported), with 315 HCs compared to 324 schizophrenic patients (SC), and 161 activation foci.

## 2.2.5 | Neural bases of mentalizing in autistic patients versus HCs

We started our search of the relevant literature by searching for studies on autistic patients in our database of 1,092 studies on the neural bases of mentalizing (see Section 2.2.1). This survey, resulting in 13 studies, was then expanded by searching for "autism theory of mind fMRI" on Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed/>) (see Figure S5). After duplicate removal, a preliminary pool of 109 studies was first screened by title, and then by abstract. While the methodological selection criteria are the same as in Section 2.2.4 (1-3), here we selected only studies reporting stronger brain activations, interpreted

by the authors as related to empathic processing, in HCs compared with autistic individuals. To this purpose, we selected only:

4. studies reporting significantly different brain activations across HCs and autistic patients (HC > ASD). In keeping with previously published meta-analyses on this disorder (e.g., Clements et al., 2018; Fernandes, Cajao, Lopes, Jeronimo, & Barahona-Correa, 2018), we included both studies on Autism and Asperger syndrome. All patients were diagnosed using the Autism Diagnostic Observational Schedule (ADOS; Lord et al., 2000) and/or the Autism Diagnostic Interview (ADI or ADI-R; Lord, Rutter, & Le Couteur, 1994), and/or using the clinical criteria reported in the DSM-IV or DSM-IV-TR, and/or in the Statistical Classification of Disease and Related Health Problems (ICD-10);

5. studies investigating brain activity related to representing another's mental states (as described in Section 2.2.1). Namely, we selected contrasts aimed to elicit brain activations interpreted in terms of a "mentalizing" or "ToM" network underpinning the representation or attribution of mental states.

Starting from an initial screening of 109 titles and abstracts, 30 papers deemed as potentially relevant were fully reviewed based on the aforementioned selection criteria (see Figure S5). We thus excluded: 2 review or meta-analysis articles; 2 studies employing techniques other than fMRI; 1 study without autistic patients; 5 studies using ROIs or SVC and 13 studies focused on processes other than mentalizing.

We included studies fulfilling the above criteria regardless of: (a) sensory modality (e.g., visual or auditory), (b) experimental paradigm (e.g., comprehension or attentional tasks), and (c) stimulus type (e.g., videos, photos, or verbal materials). Our aim was indeed to pool across different experimental paradigms to ensure both generalizability and consistency of results, within the requirement of mentalizing in autistic patients compared with HCs inherent in our research question (Radua & Mataix-Cols, 2012). This selection phase resulted in seven studies fulfilling our criteria.

We then expanded our search for other potentially relevant studies by carefully examining both the studies quoting, and those quoted by, each of these papers. This second phase highlighted eight further studies fitting our search criteria. Overall, this procedure led to include in the ALE meta-analysis 15 previously published studies (see Table S5), resulting from 15 experiments (individual comparisons reported), with 280 HCs compared to 277 autistic patients (ASD), and 88 activation foci.

## 2.2.6 | Neural bases of empathic processing in autistic patients versus HCs

We started our search of the relevant literature by searching for studies on autistic patients in our database of 721 studies on the neural bases of empathic processing (see Section 2.2.2). This survey, resulting in 18 studies, was then expanded by searching for "autism empathy fMRI" on Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed/>;

see Figure S6). After duplicate removal, a preliminary pool of 64 studies was first screened by title, and then by abstract. While the methodological selection criteria are the same as in Section 2.2.5 (1–4), here we selected only studies reporting stronger brain activations, interpreted by the authors as related to empathic processing, in HCs compared with autistic individuals. To this purpose, we selected only:

5. studies investigating brain activity related to the isomorphic experience of another's affective state (as described in Section 2.2.2). Namely, we selected studies requiring participants to attend to another person's emotional state, and performing contrasts aimed to elicit brain activations interpreted in terms of empathic processing.

Starting from an initial screening of 64 titles and abstracts, 37 papers deemed as potentially relevant were fully reviewed based on the aforementioned selection criteria (see Figure S6). We thus excluded: 1 review or meta-analysis article; 5 studies employing techniques other than fMRI; 3 studies without autistic patients and 14 studies explicitly focused on mentalizing.

We included studies fulfilling the above criteria regardless of: (a) sensory modality (e.g., visual or auditory), (b) experimental paradigm (e.g., comprehension or attentional tasks), (c) stimulus type (e.g., videos, photos, or verbal materials). Our aim was indeed to pool across different experimental paradigms to ensure both generalizability and consistency of results, within the requirement of empathic processing in autistic patients compared with HCs inherent in our research question (Radua & Mataix-Cols, 2012). This selection phase resulted in 14 studies fulfilling our criteria.

We then expanded our search for other potentially relevant studies by carefully examining both the studies quoting, and those quoted by, each of these papers. This second phase highlighted four further studies fitting our search criteria. Overall, this procedure led to include in the ALE meta-analysis 18 previously published studies (see Table S6), resulting from 18 experiments (individual comparisons reported) with 317 HCs compared to 289 autistic patients (ASD), and 92 activation foci.

## 2.3 | Activation likelihood estimation

We performed six distinct ALE analyses, using the GingerALE 3.0.2 software (Eickhoff et al., 2009), to identify regions consistently associated with: (1) mentalizing, (2) affective mentalizing, (3) cognitive mentalizing, (4) empathic processing, (5, 6) mentalizing and empathic processing in HCs compared with SC patients, (7, 8) mentalizing and empathic processing in autistic patients compared with HCs. We followed the analytic approach previously described by Arioli, Gianelli, et al. (2020), Arioli, Ricciardi, et al. (2020) and Arioli and Canessa (2019), based on Eickhoff et al. (2012). Importantly, the inclusion of multiple contrasts/experiments from the same set of subjects can generate dependence across experiment maps and thus decrease the validity of meta-analytic results. To prevent this issue, for each meta-analysis we adjusted for within-group effects by pooling the coordinates from all the relevant contrasts of a study into one experiment (Turkeltaub et al., 2002). The number of studies included in most

of these meta-analyses is in line with the recent prescriptions for ALE (Eickhoff et al., 2016; Muller et al., 2018), suggesting a minimum of 17 studies to ensure that results would not be driven by single experiments (see also Wu et al., 2019). Only in one analysis (i.e., mentalizing in HC versus ASD) we included less than 17 studies. However, our database is similar to those previously used by van Veluw and Chance (2014) and Wu et al. (2019) in previous meta-analyses addressing social processing.

In all meta-analyses, activation foci were initially interpreted as the centers of three-dimensional Gaussian probability distributions, to capture the spatial uncertainty associated with each individual coordinate. All coordinates were reported or converted into MNI space, using the automatic routine implemented in GingerALE. The three-dimensional probabilities of all activation foci in a given experiment were then combined for each voxel, resulting in a modeled activation (MA) map. The union of these maps produces ALE scores describing the convergence of results at each brain voxel (Turkeltaub et al., 2002). To distinguish “true” convergence across studies from random convergence (i.e., noise), the ALE scores are compared with an empirically defined null distribution (Eickhoff et al., 2012). The latter reflects a random spatial association between experiments, with the within-experiment distribution of foci being treated as a fixed property. A random-effects inference is thus invoked, by focusing on the above-chance convergence between different experiments, and not on the clustering of foci within a specific experiment. From a computational standpoint, deriving this null hypothesis involved sampling a voxel at random from each MA map, and taking the union of the resulting values. The ALE score obtained under this assumption of spatial independence was recorded, and the permutation procedure iterated 100 times to obtain a sufficient sample of the ALE null distribution. The “true” ALE scores were tested against the ALE scores obtained under the null distribution and thresholded at  $p < .05$ , corrected for cluster-level family wise error (FWE), and the cluster level threshold was set at  $p < .05$ , to identify above-chance convergence in each analysis (Eickhoff et al., 2012).

The resulting maps were then fed into direct comparisons and conjunction analyses, within GingerALE, to unveil the common and specific brain activations between: (1) cognitive mentalizing and affective mentalizing, (2) mentalizing and empathic processing, (3) cognitive mentalizing and empathic processing, and (4) affective mentalizing and empathic processing. For each comparison, a conjunction image was created, using the voxel-wise minimum value of the included ALE images, to display the similarity between datasets (Eickhoff et al., 2011). In the same analysis, two ALE contrast images were created and compared by directly subtracting one input image from the other. To correct for sampling errors, GingerALE creates such data by pooling the foci in each dataset and randomly dividing them into two new groupings equivalent in size to the original datasets. An ALE image is created for each new dataset, then subtracted from the other and compared with the true data. Permutation calculations are then used to compute a voxel-wise  $p$ -value image indicating where the values of the “true data” fall within the distribution of values in any single voxel. To simplify the interpretation of ALE



contrast images, significant ALE subtraction scores were converted to Z scores. For contrast analyses, we used a threshold set at  $p < .05$ , using 10,000 permutations, and minimum volume size of  $100 \text{ mm}^3$ .

### 3 | RESULTS

#### 3.1 | Mentalizing

Activations associated with the neural processing of mental states encompassed the precuneus and the posterior portion of the MTG bilaterally, extending in the inferior temporal gyrus in the left hemisphere, and in the superior temporal gyrus and TPJ in the right hemisphere. Further activations involved the right temporal pole, the inferior and middle frontal gyri bilaterally, and the dmPFC (see Figure 1a and Table 1).

#### 3.2 | Cognitive mentalizing

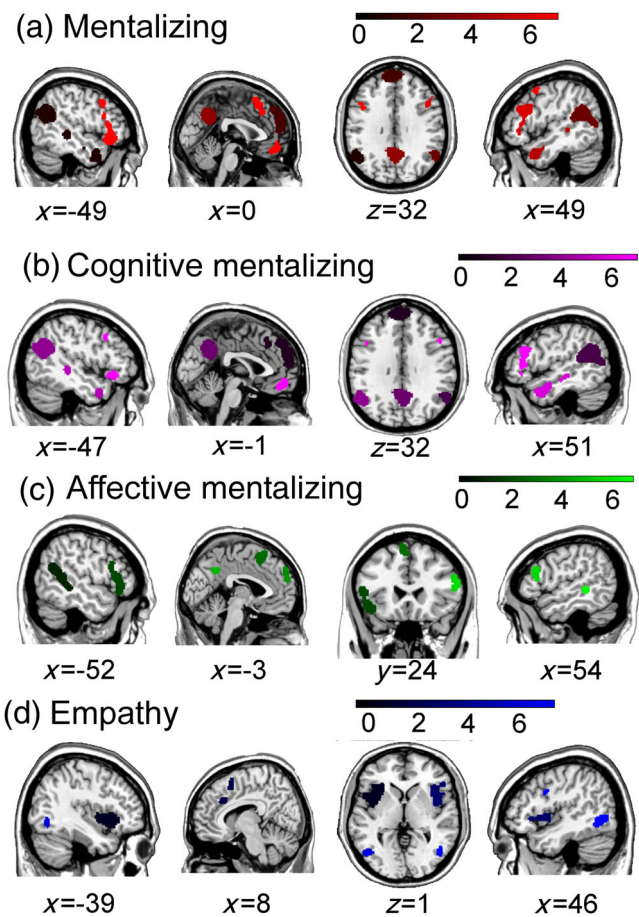
Cognitive mentalizing recruited the precuneus and the posterior sector of superior and middle temporal cortex, extending into the TPJ bilaterally, alongside more rostral sectors of the temporal lobe encompassing the left inferior temporal gyrus and right temporal pole. The left inferior and middle frontal cortex was also activated, alongside the SMA and both the dmPFC and vmPFC (see Figure 1b and Table 2).

#### 3.3 | Affective mentalizing

Making inferences on others' affective states reflected in consistent activations in the MTG bilaterally and left TPJ, alongside the precuneus bilaterally. In the frontal lobe, the SMA and the inferior and superior frontal cortex were also recruited by affective mentalizing (see Figure 1c and Table 3).

#### 3.4 | Affective and cognitive mentalizing

Common brain activations to affective and cognitive mentalizing were observed in distinct sectors of the left middle temporal and temporoparietal cortex, IFG bilaterally, alongside the SMA and the dmPFC (see Figure 2a and Table 4). Representing another's affective, compared with cognitive, mental states was associated with stronger activity in the left superior temporal pole and TPJ, MTG bilaterally, alongside the IFG bilaterally, left premotor cortex and SMA (see Figure 2a and Table 4). The reverse contrast showed that cognitive, compared with affective, mentalizing recruited the medial precuneus, the posterior sector of the MTG and the TPJ bilaterally, alongside the anterior sector of the left superior temporal cortex and the dmPFC (see Figure 2a and Table 4).



**FIGURE 1** Brain activations associated with mentalizing, cognitive mentalizing, affective mentalizing, and empathy in healthy individuals, resulting from the ALE analyses. From top to bottom, the figure reports the brain structures consistently associated with processing others' mental states (mentalizing network, red), others' cognitive mental states (cognitive mentalizing network, violet), others' affective mental states (affective mentalizing, green), as well as with empathic processing (empathy network, blue). All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE). The color bar indicates consistent brain activity intensity

#### 3.5 | Empathy

Tasks requiring an empathic processing elicited consistent bilateral activations in the frontoinsula cortex (including anterior insula, IFG, and vPMC), alongside a cluster encompassing the middle and ACC. The right postcentral and inferior temporal gyri, and the left supramarginal gyrus, were also activated, alongside the thalamus bilaterally (see Figure 1d and Table 5).

#### 3.6 | Mentalizing and empathy

A conjunction analysis highlighted commonly activated regions across empathic processing and mentalizing in the right MTG and IFG

**TABLE 1** Neural bases of mentalizing

Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
2	13,216	Medial superior frontal gyrus	0	56	28
8	4,800	Medial superior and posterior frontal gyrus	0	28	40
10	2,432	Left precentral gyrus	-36	4	46
		Left middle frontal gyrus	-44	12	36
11	1,280	Right precentral gyrus/right middle frontal gyrus	44	8	48
7	6,288	Left inferior frontal gyrus pars orbitalis	-46	26	-10
		Left inferior frontal gyrus pars triangularis	-54	24	10
6	6,736	Right inferior frontal gyrus pars triangularis	56	28	6
9	3,600	Medial prefrontal cortex	-6	50	-4
3	9,872	Right middle and superior temporal gyri	54	-52	20
		Right temporoparietal junction	52	-54	24
5	7,976	Right middle temporal gyrus	62	-24	-10
		Right middle temporal pole	52	8	-30
1	21,888	Left middle temporal gyrus	-58	-42	4
		Left inferior temporal gyrus	-46	10	-36
4	9,104	Medial precuneus	-2	-54	36

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were consistently associated with mentalizing. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE).

**TABLE 2** Neural bases of cognitive mentalizing

Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	14,376	Medial superior frontal gyrus	2	56	28
		Supplementary motor area	-4	14	58
9	1,440	Left precentral gyrus	-36	4	46
		Left inferior frontal gyrus	-46	16	36
		Left middle frontal gyrus	-42	12	48
11	1,112	Right precentral gyrus	44	8	46
8	3,248	Medial prefrontal cortex	-6	50	-6
10	1,152	Left inferior frontal gyrus	-48	24	-10
7	3,784	Right inferior frontal gyrus pars triangularis	56	26	6
		Right inferior frontal gyrus pars orbitalis	48	32	-2
4	8,848	Left superior temporal gyrus/left temporo-parietal junction	-50	-60	24
5	8,256	Left middle temporal gyrus	-56	-10	-16
		Left inferior temporal gyrus	-52	6	-28
6	5,888	Right middle temporal pole	50	8	-30
		Right middle temporal gyrus	60	-10	-18
2	10,344	Right middle temporal gyrus	54	-54	20
		Right superior temporal gyrus/right temporoparietal junction	52	-54	24
		Right middle occipital gyrus	48	-70	8
3	9,344	Left precuneus	2	-56	34

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were consistently associated with cognitive mentalizing. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE).

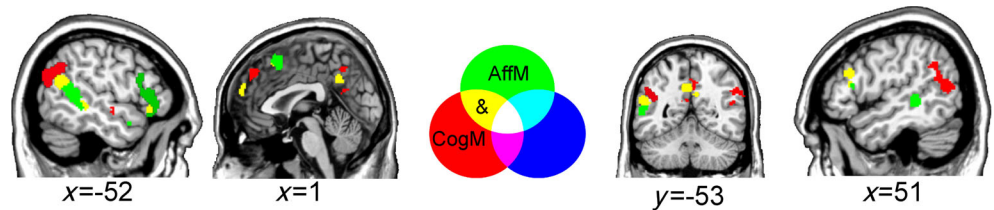
**TABLE 3** Neural bases of affective mentalizing

Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
3	3,416	Medial supplementary motor area	-4	16	56
4	2,648	Left superior frontal gyrus	-8	56	36
		Medial superior frontal gyrus	-6	58	24
5	1,384	Left precuneus	-4	-54	36
		Right precuneus/right superior frontal gyrus	8	-52	28
2	4,840	Left inferior frontal gyrus pars orbitalis	-46	26	-10
		Left inferior frontal gyrus pars triangularis	-50	18	24
6	1,296	Right inferior frontal gyrus pars triangularis	58	24	16
1	5,240	Left middle temporal gyrus/left temporoparietal junction	-52	-38	-4
8	784	Right middle temporal gyrus	52	-36	-2
7	824	Right inferior occipital gyrus	30	-94	-4

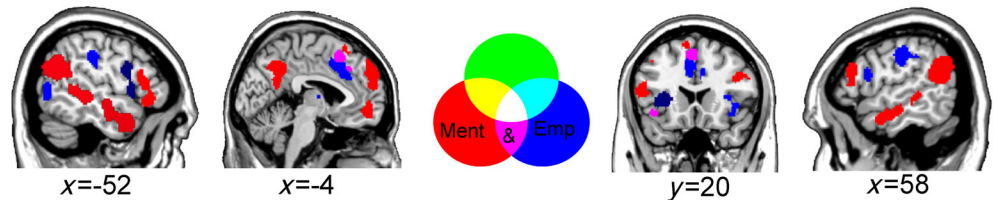
Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were consistently associated with affective mentalizing. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE).

**FIGURE 2** Commonalities and differences across mentalizing, cognitive mentalizing, affective mentalizing and empathy networks in healthy individuals, resulting from the ALE analyses. From top to bottom, the figure depicts with different colors the common and specific brain structures across cognitive mentalizing and affective mentalizing (a), mentalizing and empathy (b), cognitive mentalizing and empathy (c), as well as affective mentalizing and empathy (d). All the reported clusters survived a statistical threshold of  $p < .05$  and minimum volume size of 100 mm<sup>3</sup>. AffM, affective mentalizing; CogM, cognitive mentalizing; and Emp, empathy

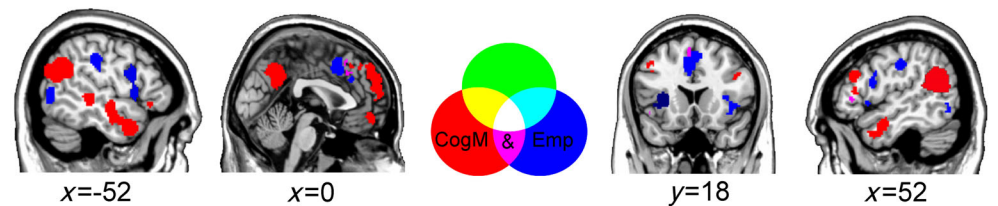
(a) Cognitive mentalizing versus affective mentalizing



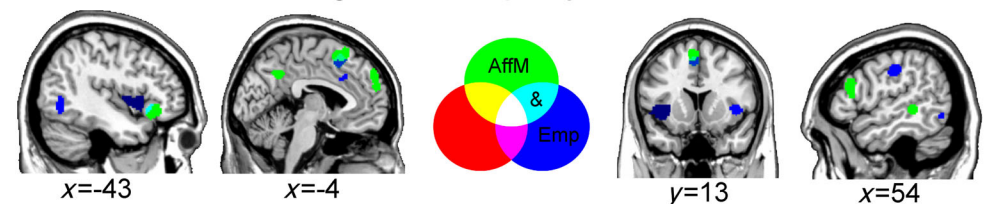
(b) Mentalizing versus empathy



(c) Cognitive mentalizing versus empathy



(d) Affective mentalizing versus empathy



bilaterally, as well as in the mPFC and SMA (see Figure 2b and Table 6). Direct comparisons revealed activations specific to mentalizing in the left precuneus and MTG bilaterally, in the right TPJ,

as well as in the dmPFC, left IFG, and both middle and superior frontal gyri bilaterally (see Figure 2b and Table 6). Instead, activations specific to an empathic processing were found in the fronto-insular cortex

**TABLE 4** Common and specific regions across the cognitive and affective mentalizing networks

Cognitive & affective mentalizing					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	2,312	Left superior frontal gyrus	-8	56	36
		Medial superior frontal gyrus	-6	58	24
3	1,320	Medial precuneus	-4	-54	36
		Right superior frontal gyrus	8	-52	28
4	1,064	Left inferior frontal gyrus pars orbitalis	-48	24	-10
6	704	Right inferior frontal gyrus pars triangularis	56	26	18
7	472	Supplementary motor area	-4	14	58
2	1,576	Left middle temporal gyrus/left temporoparietal junction	-56	-58	20
5	744	Left middle temporal gyrus	-52	-36	-4
Affective theory of mind > cognitive mentalizing					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
3	3,320	Supplementary motor area	-2	22	60
		Supplementary motor area	-8	14	46
1	4,304	Left inferior frontal gyrus pars orbitalis	-46	28	-8
		Left inferior frontal gyrus pars triangularis	-52	32	2
		Left inferior frontal gyrus pars opercularis	-52	14	22
6	648	Right inferior frontal gyrus pars opercularis	58	22	14
		Right inferior frontal gyrus pars triangularis	56	20	24
7	432	Left superior frontal gyrus	-8	56	38
9	200	Left precentral gyrus	-42	8	38
10	128	Left superior temporal pole	-50	8	-20
11	104	Left superior temporal pole	-58	-20	-4
2	3,880	Left middle temporal gyrus/left temporoparietal junction	-55	-48	8
5	776	Right middle temporal gyrus	48	-38	2
8	328	Left cuneus	-10	62	22
4	816	Right inferior occipital gyrus	32	-94	-10
Cognitive mentalizing > affective mentalizing					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
4	920	Medial superior frontal gyrus	4	44	42
6	104	Left superior temporal gyrus	-52	-8	-6
		Left middle temporal gyrus	-50	-10	-10
1	4,472	Left middle temporal gyrus/left temporoparietal junction	-45	-65	23
2	2,240	Right middle temporal gyrus/right temporoparietal junction	48	-66	12
		Right angular gyrus	54	-50	34
5	192	Right middle temporal gyrus	60	-22	-11
3	2,024	Medial precuneus	4	-58	46
		Left cuneus	-10	-60	21

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were commonly (top) and specifically (bottom) associated with the cognitive and affective mentalizing networks. All the reported clusters survived a statistical threshold of  $p < .05$  and minimum volume size of 100 mm<sup>3</sup>.

bilaterally, alongside the ACC and the SMA in the medial wall. Further empathy-related activations involved the postcentral gyrus, extending into the supramarginal gyrus, as well as the inferior temporal cortex and the thalamus bilaterally (see Figure 2b and Table 6).

### 3.7 | Cognitive mentalizing and empathy

Common activations to empathy and cognitive mentalizing were identified in the right MTG and IFG bilaterally, as well as in a cluster

**TABLE 5** Neural bases of empathic processing

Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	11,384	Left insula	-30	22	6
		Left inferior frontal gyrus pars opercularis	-54	8	20
		Left precentral gyrus	-56	10	24
		Left inferior frontal gyrus pars orbitalis	-38	26	-2
3	4,864	Right insula	42	10	0
		Right inferior frontal gyrus pars triangularis	52	30	0
9	1,280	Right inferior frontal gyrus pars opercularis	54	10	18
		Right precentral gyrus	48	6	30
2	9,176	Middle cingulate gyrus	-4	14	44
		Right cingulate gyrus	8	24	34
		Right supplementary motor area	8	12	52
		Middle supplementary motor area	6	12	62
7	1,720	Right inferior temporal gyrus	48	-66	-2
		Right fusiform gyrus	44	-60	-8
5	3,416	Right postcentral gyrus	62	-20	36
4	4,840	Left supramarginal gyrus	-58	-26	36
6	2,296	Left inferior occipital gyrus	-46	-68	-4
8	1,520	Left thalamus	-10	-12	8
		Right thalamus	10	-18	10

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were consistently associated with empathic processing. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE).

encompassing the SMA and dmPFC (see Figure 2c and Table 7). Compared with empathic processing, cognitive mentalizing was associated with stronger bilateral activity in both the posterior and anterior sectors of middle temporal gyrus, as well as in the right superior temporal gyrus and TPJ, inferior and middle frontal cortex, alongside the dmPFC (see Figure 2c and Table 7). The reverse comparison highlighted stronger bilateral activity for empathic processing than mentalizing in the supramarginal gyrus, inferior frontal, and precentral gyri, anterior insula and ACC, alongside the caudate (see Figure 2c and Table 7).

### 3.8 | Affective mentalizing and empathy

A conjunction analysis unveiled common activity across affective mentalizing and empathic processing in the SMA and left IFG (see Figure 2d and Table 8). Compared with empathic processing, affective mentalizing elicited stronger activity in the precuneus, middle temporal and inferior frontal gyri bilaterally, SMA, and dmPFC (see Figure 2d and Table 8). Conversely, empathic processing was associated with greater bilateral activity in the supramarginal and middle temporal gyri, anterior insula, and middle-ACC, alongside the left precentral and right postcentral gyri (see Figure 2d and Table 8).

### 3.9 | Mentalizing and empathic processing in SC patients

Compared with controls, schizophrenic patients displayed decreased activity in the left MTG in association with mentalizing tasks (see Figure 3 and Table 9). Instead, no significant difference between SC patients and controls was found in association with empathic processing.

### 3.10 | Mentalizing and empathic processing in autistic patients

Compared with controls, autistic patients displayed decreased activity of the left posterior MTG (Figure 3 and Table 10) and right parahippocampal gyrus (Figure 3 and Table 11) in association with mentalizing and empathic processing, respectively.

## 4 | DISCUSSION

Over two decades of neuroimaging and behavioral research have produced considerable evidence, and a variety of theoretical perspectives, on the neurocognitive processes underlying the human ability to



**TABLE 6** Common and specific regions across the mentalizing and empathy networks

Mentalizing & empathy					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
3	264	Medial superior frontal gyrus	-2	28	38
1	1,368	Medial supplementary motor area	-4	18	50
2	376	Left inferior frontal gyrus pars orbitalis	-42	24	-4
4	240	Right inferior frontal gyrus pars triangularis	52	30	0
5	16	Right middle temporal gyrus	48	-70	4
Mentalizing > empathy					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
2	9,040	Medial superior frontal gyrus	-5	57	36
		Left superior frontal gyrus	-20	56	30
		Right superior frontal gyrus	11	55	28
11	776	Left superior and posterior frontal gyrus	-6	26	60
13	144	Medial superior frontal gyrus	2	30	46
8	2,168	Medial middle frontal gyrus	0	56	-10
		Left middle frontal gyrus	-10	50	-4
9	1,464	Left precentral gyrus	-40	10	44
		Left middle frontal gyrus	-46	14	44
10	952	Right middle frontal gyrus	40	8	53
6	3,688	Left inferior frontal gyrus pars triangularis	-57	24	10
		Left inferior frontal gyrus pars orbitalis	-50	28	-7
7	3,584	Right inferior frontal pars triangularis	57	29	26
1	18,912	Left middle temporal gyrus	-54	-39	4
3	8,200	Right middle temporal gyrus/right temporoparietal junction	54	-56	22
5	5,488	Right middle temporal gyrus	56	-32	-4
		Right middle temporal pole	54	12	-32
4	8,200	Left precuneus	2	-55	37
12	208	Left caudate/putamen	-13	8	-10
Empathy > mentalizing					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	8,424	Left insula	-38	6	-1
		Left inferior frontal gyrus pars opercularis	-48	13	16
4	3,472	Right insula	36	22	8
10	224	Left inferior frontal gyrus pars orbitalis	-30	28	-10
7	1,192	Right inferior frontal gyrus pars opercularis	58	9	21
		Right precentral gyrus	48	4	28
2	5,816	Left cingulate gyrus	-4	14	41
		Medial supplementary motor area	0	9	45
		Right supplementary motor area	12	12	48
		Right anterior cingulate gyrus	8	24	28
		Left anterior cingulate gyrus	-8	26	30
6	2,168	Left inferior temporal gyrus	-48	-67	-4
8	744	Right fusiform gyrus	50	-70	-8
		Right inferior temporal gyrus	54	-66	-10
		Right middle temporal gyrus	48	-64	0
3	4,840	Left supramarginal gyrus	-59	-24	31

TABLE 6 (Continued)

Empathy > mentalizing					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
5	3,408	Right postcentral gyrus	60	-19	35
		Right supramarginal gyrus	58	-32	36
9	272	Right thalamus	10	-14	8
		Left thalamus	-12	-6	8
11	112	Right caudate	8	10	-2

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were commonly (top) and specifically (bottom) associated with the mentalizing and empathy networks. All the reported clusters survived a statistical threshold of  $p < .05$  and minimum volume size of 100 mm<sup>3</sup>.

understand other minds. The increase of available knowledge, however, has paralleled a growing awareness of several inconsistent views about fundamental issues such as the classification of distinct processes of social understanding, their definitions and, even more important, their common and/or specific neuro-cognitive bases (Happé et al., 2017; Schaafsma, Pfaff, Spunt, & Adolphs, 2015; Spunt & Adolphs, 2017). While the discussion on the building blocks of social understanding mainly revolves around the notions of empathy, affective mentalizing, and cognitive mentalizing, their degree of overlap versus specificity is still debated (Cerniglia et al., 2019). We investigated for the first time their common versus specific neural correlates via a coordinate-based meta-analytic approach highlighting both the most consistent activations in HCs, and the most consistent alterations of brain activity in two disorders characterized by marked social communicative impairments such as SC and autism.

#### 4.1 | Neural bases of mentalizing and empathy

The present results provide novel evidence for the existence of two distinct networks of areas associated with mentalizing and empathy. Processing others' mental states in terms of abstract inferences was associated with the consistent engagement of the mPFC and precuneus in the midline, alongside the middle and superior temporal gyri, extending into the TPJ, bilaterally (Arioli & Canessa, 2019; Molenberghs et al., 2016; van Veluw and Chance, 2014). A considerable literature provided cues into the role of the key nodes of this network, and particularly the dmPFC, previously associated with perspective-taking and episodic memory retrieval (Geiger et al., 2019), and the pSTS, involved in coding biological motion alongside the underlying intentionality (Dasgupta, Tyler, Wicks, Srinivasan, & Grossman, 2017) and social significance (Arioli, Basso, Poggi, et al., 2021). A critical question concerns whether these regions play a unique role in processing goals and intentions (Gao, Geng, Li, Zhou, & Yao, 2018), or rather underpin more basic functions required by mentalizing. According to the former view, TPJ might underpin transient mental inferences about people such as their goals, desires and beliefs (Lamm, Batson, & Decety, 2007; Saxe & Kanwisher, 2003), whereas the mPFC would subserve the attribution of more general

traits and qualities about the self and other people (Van Overwalle, 2009). However, the recruitment of temporoparietal regions by tasks involving the reorientation of attention and a sense of agency (Sperduti, Delaveau, Fossati, & Nadel, 2011) has prompted an alternative—and controversial (e.g., Geng & Vossel, 2013)—interpretation of their role in terms of attentional reorienting (Dugue, Merriam, Heeger, & Carrasco, 2018). Based on recent evidence of its involvement in processing the polarity, complexity and intensity of the emotional experience (Lettieri et al., 2019), TPJ might also contribute to mentalizing by generating abstract representations of emotions, which might then underpin the coding of perceived affective states as—for instance—pleasant, unpleasant or ambivalent. Finally, the precuneus has been suggested to underpin the construction of different perspectives during social mentalizing tasks, through mental imagery supported by episodic memory retrieval and autobiographical memory (Hebscher, Levine, & Gilboa, 2018; Schurz et al., 2020).

Interestingly, the aforementioned regions largely overlap with the key nodes of the default mode network (DMN). While being traditionally considered an “intrinsic” system associated with *internally oriented* cognitive processes such as self-referential thinking, daydreaming, reminiscing and future planning (Raichle, 2015), the DMN also appears to be involved in thinking about other people's beliefs, intentions and motivations (Yeshurun, Nguyen, & Hasson, 2021). In this view, the DMN contributes to representing mental states by underpinning the retrieval of a pool of prior experiences, which support the interpretation of affects and beliefs in the light of the current context (Mars et al., 2012). This process involves abstraction skills, which the DMN is well-suited to support based on its structural and functional connectivity (FC; Finlay & Uchiyama, 2015; Satpute & Lindquist, 2019). If the DMN plays a key role in enabling abstraction, its involvement should be decreased when the latter is less needed to represent mental representation. This would be the case of the empathic response, in which the understanding of others' experiences is mediated by emotional sharing rather than abstract inferences.

Indeed, tasks tapping an empathic processing consistently recruited other brain regions, such as anterior-middle cingulate, fronto-insular and postcentral regions, which seem to underpin the multiple facets of sharing others' experiences (Timmers et al., 2018). The anterior-middle cingulate cortex (extending caudally into the SMA)

**TABLE 7** Common and specific regions across the cognitive mentalizing and empathy networks

Cognitive mentalizing & empathy					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	384	Supplementary motor area	-4	22	50
6	8	Medial supplementary motor area	-2	14	58
2	176	Medial superior frontal gyrus	0	26	38
4	112	Left inferior frontal gyrus pars orbitalis	-44	22	-10
3	128	Right inferior frontal gyrus pars orbitalis	50	30	-2
		Right inferior frontal gyrus pars triangularis	54	26	2
5	16	Right middle occipital gyrus	48	-70	4
Cognitive mentalizing > empathy					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
2	8,688	Medial superior frontal gyrus	-3	58	36
		Left superior frontal gyrus	-18	56	32
		Right middle frontal gyrus	6	52	8
		Right prefrontal cortex	10	52	14
3	8,400	Medial superior frontal gyrus/medial precuneus	3	-56	38
9	864	Left middle frontal gyrus	-44	14	44
		Left precentral gyrus	-40	10	44
		Left inferior frontal gyrus pars opercularis	-42	16	34
10	864	Right middle frontal gyrus	40	6	54
12	160	Left inferior frontal gyrus pars orbitalis	-52	26	-8
11	216	Right inferior frontal gyrus pars triangularis	52	26	10
8	1,312	Right inferior frontal gyrus pars triangularis	55	29	28
		Right inferior frontal gyrus pars opercularis	48	22	32
7	2,008	Medial anterior cingulate	4	56	-12
		Medial frontal gyrus	0	56	-10
		Left anterior cingulate	-10	48	-4
4	7,648	Left middle temporal gyrus	-57	-20	-10
5	7,360	Left middle temporal gyrus	-49	-64	24
6	3,992	Right middle temporal gyrus	62	-28	-8
		Right inferior temporal gyrus	58	-16	-20
1	8,696	Right middle and superior temporal gyrus/right temporoparietal junction	54	-56	22
		Right angular gyrus	54	-52	30
Empathy > cognitive mentalizing					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	8,104	Left insula	-39	17	8
		Left precentral gyrus	-54	7	15
4	3,376	Right insula	36	22	8
2	6,128	Medial supplementary motor area	0	12	46
		Left anterior cingulate	-7	28	26
		Right anterior cingulate	10	24	28
12	104	Left inferior frontal gyrus pars orbitalis	-30	28	-10
7	1,192	Right inferior frontal gyrus pars opercularis	59	11	13
		Right precentral gyrus	46	2	34
9	440	Right fusiform gyrus	48	-70	-8
		Right middle temporal gyrus	44	-64	0

TABLE 7 (Continued)

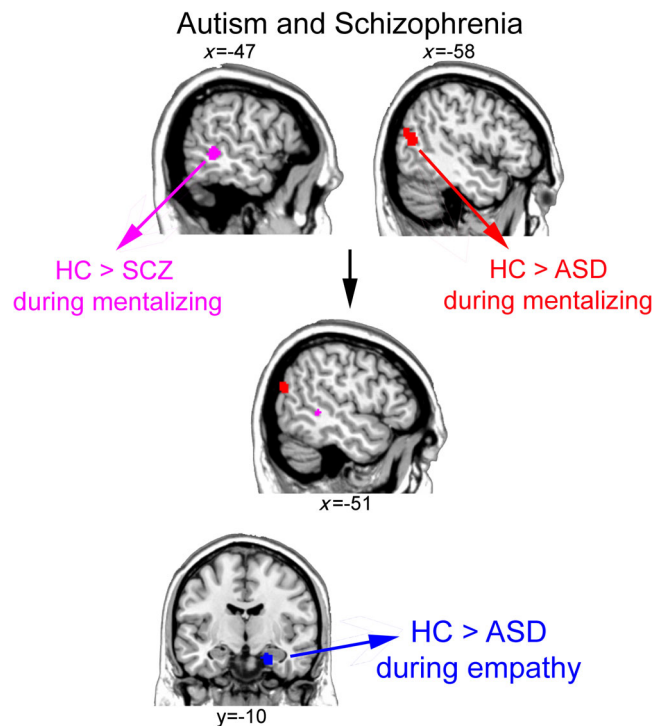
Empathy > cognitive mentalizing					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
3	4,840	Left supramarginal gyrus	-59	-23	31
5	3,368	Right supramarginal gyrus	60	-19	35
6	2,080	Left inferior occipital gyrus	-49	-68	-4
8	472	Left thalamus	-16	-16	8
10	200	Right thalamus	10	-12	8
11	168	Right caudate	10	10	0

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were commonly (top) and specifically (bottom) associated with the cognitive mentalizing and empathy networks. All the reported clusters survived a statistical threshold of  $p < .05$  and minimum volume size of 100 mm<sup>3</sup>.

TABLE 8 Common and specific regions across the affective mentalizing and empathy networks

Affective mentalizing & empathy					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	1,520	Medial supplementary motor area	-4	18	54
2	232	Left inferior frontal gyrus pars orbitalis	-44	22	-8
Affective mentalizing > empathy					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
3	2,368	Medial supplementary motor area	-7	21	59
4	2,328	Left superior frontal gyrus	-8	57	38
		Medial superior frontal gyrus	-5	59	23
2	4,568	Left inferior frontal gyrus pars orbitalis	-49	29	-8
		Left inferior frontal gyrus pars triangularis	-53	24	9
5	1,280	Right inferior frontal gyrus pars triangularis	58	26	22
1	5,096	Left middle temporal gyrus	-56	-45	4
7	712	Right middle temporal gyrus	51	-36	-5
6	1,264	Left precuneus	-7	-58	39
		Medial precuneus	-4	-54	40
		Right precuneus	7	-51	30
8	488	Right lingual gyrus	29	-98	-1
9	120	Right inferior frontal gyrus	58	32	4
Empathy > affective mentalizing					
Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	5,256	Left insula	-40	7	-1
4	2,480	Right insula	41	11	1
8	944	Left precentral gyrus	-56	2	22
6	1,488	Right anterior cingulate	10	23	30
		Right middle cingulate	8	26	32
5	1,752	Left middle temporal gyrus	-52	-66	2
		Left fusiform gyrus	-46	-64	-6
7	968	Right middle temporal gyrus	48	-60	0
		Right inferior temporal gyrus	54	-64	-6
2	4,688	Left supramarginal gyrus	-63	-22	26
3	3,416	Right postcentral gyrus	58	-21	33
		Right supramarginal gyrus	64	-21	30

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were commonly (top) and specifically (bottom) associated with the affective mentalizing and empathy networks. All the reported clusters survived a statistical threshold of  $p < .05$  and minimum volume size of 100 mm<sup>3</sup>.



**FIGURE 3** Differential brain responses to mentalizing and empathic processing between schizophrenic or autistic patients and healthy controls, resulting from the ALE analyses. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE)

and the insula (extending into the IFG) are the key nodes of the interoceptive awareness system and might thus underlie the neural representation of both one's own and others' emotional states (Berntson & Khalsa, 2021). This evidence strengthens the view of the insula as input region of the empathy network, translating sensations into subjective feelings and awareness (Medford & Critchley, 2010; Naor et al., 2020), whereas the ACC might represent the output region modulating empathy-related behavioral drives. The latter interpretation fits with the causal role of the ACC in the affective and motivational aspects of first-hand pain (Marsh, 2018), strengthened by the evidence of its role in social situations characterized by negative emotions (i.e., forgiveness; Ricciardi et al., 2013) and social pain (Eisenberger, 2015). This interpretation is in line with evidence reporting no decreased performance (i.e., accuracy and reaction time) when processing others' pain in patients with cingulate cortex lesions (Gu et al., 2012). Indeed, only the motivational facets of the empathic response seem to be impaired with cingulate dysfunctions.

Our findings therefore appear to support simulation theories, according to which a direct understanding of others' emotions is mediated by a neural mechanism of embodied simulation producing an “as-if” experience mediated by shared body states (Ciaunica, 2019; Gallese, 2019). The joint engagement of the anterior insular and ACCs might then allow an integrated awareness of the sensory, affective, and cognitive facets of the overall empathetic response. It is worth noting that the role of anterior insula and ACC as key nodes of the so-called “salience network,” through which the detection of behaviorally

Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	1,080	Left middle temporal gyrus	-46	-66	12

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima and anatomical labeling of the clusters which were consistently associated with mentalizing in healthy controls compared with schizophrenic patients. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE).

**TABLE 9** Neural bases of mentalizing in healthy controls compared with schizophrenic patients

**TABLE 10** Neural bases of mentalizing in healthy controls compared with autistic patients

Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	864	Left middle temporal gyrus/left temporo parietal junction	-56	-42	0

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were consistently associated with mentalizing in healthy controls compared with autistic patients. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE).

**TABLE 11** Neural bases of empathic processing in healthy controls compared with autistic patients

Cluster #	Cluster size (mm <sup>3</sup> )	Brain region	x	y	z
1	784	Right parahippocampal gyrus/right amygdala	22	-10	-26

Note: From left to right, the table reports the size (in mm<sup>3</sup>), stereotaxic coordinates of local maxima, and anatomical labeling of the clusters which were consistently associated with empathic processing in healthy controls compared with autistic patients. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FEW).



relevant stimuli activates controlled processes (Arioli, Basso, Carne, Poggi, et al., 2021; Uddin, 2015), has prompted alternative accounts of their engagement as reflecting the shared saliency of the stimuli (Valentini & Koch, 2012).

## 4.2 | Neural bases of affective and cognitive mentalizing and empathy

In this paragraph, we will initially present the results on the specific and common activations between affective and cognitive mentalizing, showing how social information is integrated in the two networks. Next, we will analyze the interaction between these two networks and the empathy system, trying to highlight the points of possible communication between these circuits.

The affective and cognitive subcomponents of mentalizing elicited consistent common activity in most of the aforementioned nodes of the mentalizing network, that is, left posterior middle temporal and temporoparietal cortex, IFG bilaterally, alongside the dmPFC and posterior-medial frontal cortex (Arioli & Canessa, 2019; Geiger et al., 2019). These common activations support Shamay-Tsoory et al.'s (2010) proposal that both ToM sub-conditions require a more basic mentalizing ability, which is likely paralleled by condition-specific activations (Molenberghs et al., 2016).

Indeed, affective mentalizing was also associated with stronger activity than its cognitive counterpart in the left superior and middle temporal pole, alongside the SMA and the IFG. This finding fits the demands placed by affective ToM tasks, typically involving pictures or videos of emotional expressions which are expected to activate simulation routines associated with the frontal sector of the action observation network (Rizzolatti & Sinigaglia, 2010), possibly in conjunction with affectively enriched signals from the temporopolar cortex (Geiger et al., 2019; Van Overwalle & Baetens, 2009). While this pattern suggests that even affective ToM might involve visceral emotional reactions mediated by simulation routines (Winkielman, Coulson, & Niedenthal, 2018), the activations associated with cognitive mentalizing are more suggestive of higher-order abstract reasoning detached from viscerosensory processing (Molenberghs et al., 2016). Stronger activation for cognitive than affective ToM was indeed found in the TPJ, precuneus and dmPFC, whose role in representing cognitive mental states such as beliefs, goals and intentions (Van Overwalle & Baetens, 2009) is now interpreted in the light of the possible DMN role in self-projection (Spreng & Mar, 2012). Indeed, the DMN is nowadays considered a “sense-making” network that integrates incoming extrinsic inputs with prior intrinsic information to form rich, context-dependent models of dynamic social situations between the self and others (Li, Mai, & Liu, 2014). This kind of processing appears particularly relevant for cognitive mentalizing, in which the need to distinguish between appearance and reality, via abstract representations of the situational context, might involve key nodes of the DMN (Yeshurun et al., 2021) and particularly the precuneus (Schlaffke et al., 2015), which supports episodic memory retrieval and autobiographical memory (Hebscher et al., 2018; Schurz

et al., 2020). The present results provide novel insights into the relationship between affective and cognitive mentalizing, by suggesting a gradient of activations associated with the two processes in the left posterior lateral temporal cortex. This functional subdivision involves three adjacent clusters encompassing the left posterior MTG, STS, and TPJ, associated with affective-specific (green), overlapping cognitive-affective (yellow), and finally cognitive-specific (red; Figure 2a) activity, which might underpin the transition between the processing of the affective facets of mental states and their neural coding in terms of abstract cognitive representations detached from sensory aspects. While further evidence is required to unveil the possible functional meaning of this gradient, it is noteworthy that similar brain activations have been previously reported using both verbal (Sebastian et al., 2012) and visual (Schlaffke et al., 2015) stimuli. Moreover, previous studies highlighted a prominent role of the dorsal and anterior/ventral TPJ sector in processing, respectively, false beliefs and trait judgments (i.e., cognitive mentalizing) and social animations or gaze at the RMET (i.e., affective mentalizing; Schurz et al., 2014). Alongside our evidence on a gradient of posterior temporal activity for these different facets of mentalizing, such pattern reflects the “overarching view” model of functional specialization (Cabeza, Ciaramelli, & Moscovitch, 2021), i.e., *graded*, rather than segregated, functional subdivisions associated with specific facets of a global cognitive function supported by a broader region. These observations are consistent with Lettieri et al.'s (2019) evidence that moment-by-moment ratings of perceived emotions explain brain activity in TPJ, with orthogonal and spatially overlapping TPJ gradients encoding the polarity, complexity, and intensity of emotional experiences. The spatial arrangement of these gradients is thus well-suited to map a variety of mental and affective states within TPJ. Taken together, these findings might thus suggest that the subregion-specific processing of affective versus cognitive information about a person might provide a graded contribution to a more general “mentalizing” function expressed in MTG/TPJ through an attentional re-orienting to mental and affective states (Schurz et al., 2014).

The output of this process might be then relayed to the medial frontal cortex, which has been suggested to play a role in forming impressions of people (Mattavelli et al., 2011; Ferrari et al., 2016) and in their accuracy (Spunt & Adolphs, 2014; Wagner, Kelley, Haxby, & Heatherton, 2016). Also in the dmPFC, indeed, we observed a rostro-caudal gradient of activity associated with both cognitive and affective mentalizing in its rostral-most sector (Figure 2a; yellow), followed caudally by cognitive mentalizing (red), and finally by affective mentalizing (green) in the SMA. This progression fits with the dmPFC role in the cognitive proper aspects of mentalizing (Sebastian et al., 2012), that is, when this process does not involve emotional cues which rather seem to engage the vmPFC (Schlaffke et al., 2015). Interestingly, the dorsomedial regions involved in this transition surround a large anterior/middle cingulate cluster, which is consistently associated with empathic processing (Lamm et al., 2011). The partial overlap between the latter cluster and those associated with the gradient from cognitive to affective mentalizing (Figure 2c,d) suggests that an empathic processing might provide signals allowing a

progressive transition from the abstract representation of cognitive mental states detached from sensory facets to emotionally-charged representations of affective mental states (Figure 4; blue). This progressive integration of different facets of social information fits with the strong connectivity pattern between the posterior medial frontal cortex and premotor, SMA and cingulate motor areas, which has been suggested to underpin tasks tapping action monitoring and attention (Amodio & Frith, 2006), but also mentalizing (Molenberghs et al., 2016).

An analogous mosaic of areas belonging to these three systems, possibly underpinning a reciprocal exchange of information, was also found in the inferior frontal cortex, bilaterally. In the left hemisphere we observed a mosaic of activations associated with empathy-specific activity in the left anterior insula (blue; Figures 2d and 4), overlapping empathy-affective mentalizing (cyan; Figure 2d), as well as cognitive-affective mentalizing (yellow; Figure 4) and finally affective mentalizing-specific (green; Figures 2d and 4) activations in adjacent sector of the left IFG. Such an involvement of fronto-insular regions for distinct facets of social understanding is in keeping with considerable evidence of its engagement when representing others' mental states, both in healthy individuals (Grecucci, Giorgetta, Bonini, & Sanfey, 2013) and in pathological conditions such as anorexia nervosa (McAdams, Harper, & Van Enkevort, 2018). In the right hemisphere, we observed mainly distinct activations associated with empathy-specific processing in the caudal IFG (blue; Figure 4), and with cognitive and affective mentalizing in its dorsal (red; Figure 4) and rostral (green; Figure 4) sectors, respectively. This functional segregation allows to refine previous reports of the right IFG involvement in both affective mentalizing and empathy (Hooker, Verosky, Germine, Knight, & D'Esposito, 2008). This region has been consistently associated with a variety of social cognitive processes, including emotional contagion and emotion recognition (Schurz et al., 2014), and its common engagement by empathy and affective mentalizing supports the possible contribution of simulation processes both to a direct, and a

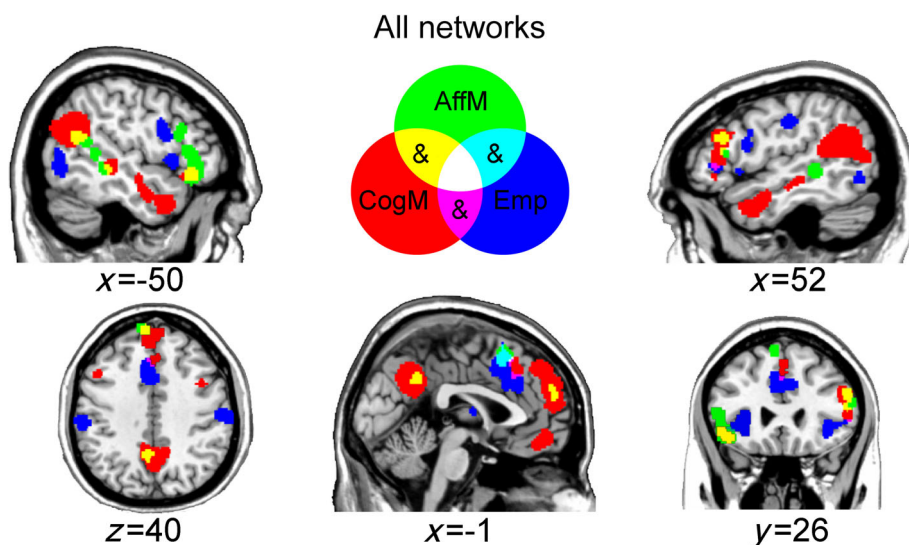
cognitively-mediated, understanding of others' feeling and emotional mental states (Molenberghs et al., 2016).

Altogether, these patterns of activation appear to support Shamay-Tsoory et al.'s (2010) proposal that affective mentalizing builds on both the output of cognitive mentalizing and an empathic processing. However, while that model suggests that cognitive mentalizing and empathy provide independent contributions to affective mentalizing, the present data fit a more naturalistic form of social cognition characterized by networks of adjacent areas underlying interconnected sub-processes, which support a more general ability of affective mentalizing. Moreover, the present results provide evidence for Schurz et al.'s (2020) hierarchical model, confirming the existence of three different clusters underlying social cognition corresponding to cognitive, affective mentalizing and empathy.

### 4.3 | Neural bases of altered mentalizing and empathy in SC and ASD

Building on the results from healthy individuals, we aimed to unveil the most consistent patterns of altered empathy- or ToM-related brain activity in SC and ASD. Importantly, the heterogeneity of neuroimaging results from such pathological populations (Martinez-Murcia et al., 2017) likely reflects the considerable heterogeneity of their clinical manifestation (Alnaes et al., 2019; Mottron & Bzdok, 2020), ranging from mild to profound (de Vries & Geurts, 2015), as well as at their etiology (Jeste & Geschwind, 2014) and the associated pharmacological treatments (Masi et al., 2017).

In line with recent meta-analytic evidence of abnormal activity in the key sectors of the "social brain" in SC (Vucurovic et al., 2020), the weaker ToM-related activation displayed by patients than HC in the left posterior MTG and TPJ (Figure 3) allows to constrain the widespread pattern of altered brain responses previously associated with SC (e.g., Zhao et al., 2018). This observation fits with Kuroki



**FIGURE 4** Commonalities and differences across cognitive mentalizing, affective mentalizing, and empathy networks in healthy individuals, resulting from the ALE analyses. Cognitive mentalizing, affective mentalizing, and empathy networks in this figure are superimposed onto the same brain render and slices. All the reported clusters survived a statistical threshold of  $p < .05$ , corrected for cluster-level family wise error (FWE). AffM, affective mentalizing; CogM, cognitive mentalizing; and Emp, empathy

et al.'s (2006) neurostructural evidence of decreased gray matter (GM) volume of the left and right MTG in first episode SC (see also Onitsuka et al., 2004) but not in first episode affective psychosis. Indeed, these data led to consider GM volume of the left posterior MTG, which additionally discriminates patients and unaffected siblings from controls (Guo et al., 2014), as a biomarker for SC.

Importantly, we found no consistent evidence in schizophrenic patients of abnormal activity in association with tasks requiring an empathic processing. While this negative finding might appear in conflict with previous meta-analytic report of altered activity in the empathy network (Vucirovic et al., 2020), it is noteworthy that Vucirovic et al (2020) included in their "empathy" condition studies focused explicitly on affective mentalizing (e.g., Mier et al., 2010). Indeed, several individual studies reported no clear-cut evidence of altered brain activity and behavioral performance in schizophrenic patients attending to others' pain (Horan et al., 2016; Vistoli, Lavoie, Sutliff, Jackson, & Achim, 2017) or emotions (Caruana, Stein, Watson, Williams, & Seymour, 2019; Torregrossa et al., 2019). Lehmann et al. (2014) have provided a more detailed characterization of schizophrenic patients' defective understanding of others' emotions (i.e., affective mentalizing), associated with a preserved ability to share or feel their emotional states (i.e., empathy). The latter finding is further supported by recent evidence of preserved emotional empathy in self-reported and behavioral measurements in schizophrenic patients (Berger et al., 2019). Overall, the present findings appear to highlight a possible neural basis of a specific deficit in mentalizing, with no clear evidence of abnormal empathic processing in schizophrenic patients.

When engaged in mentalizing tasks, ASD patients displayed weaker activity than HCs in the left posterior MTG, although in a more rostral sector compared with the cluster previously reported for schizophrenic patients (Figure 3). There is multifaceted evidence for a role of this region in ASD patients' defective social understanding. First, autistic patients displayed altered MTG and TPJ activity during irony processing (Wang, Lee, Sigman, & Dapretto, 2006) and mentalizing in a social context (Assaf et al., 2013; Sato, Toichi, Uono, & Kochiyama, 2012). Moreover, decreased resting state FC has been reported, in ASD, between the bilateral MTG and cerebellum (Ramos-Cabo et al., 2019). Finally, both in children and adults with ASD the degree of hypo-connectivity between posterior MTG and other regions, including key nodes of the social brain such as IFG and precuneus, has been shown to reflect the severity of social cognitive and language deficits (Xu et al., 2020).

Interestingly, an association between altered MTG response and defective mentalizing in both autism and SC has been previously suggested, but never supported by empirical evidence (e.g., Sugranyes, Kyriakopoulos, Corrigan, Taylor, & Frangou, 2011). In this respect, growing evidence highlights the involvement of posterior temporal areas both in the "mentalizing" (Moessnang et al., 2017; Walbrin & Koldewyn, 2019) and default mode (Hyatt et al., 2020) networks. Impaired DMN FC (a measure of synchronous neural activity between remote brain areas that define neural networks) has been shown in SC and ASD (Hu et al., 2017; Padmanabhan, Lynch, Schaer, & Menon, 2017), and associated with social functioning and cognitive

deficits in these disorders (Fox et al., 2017). Additionally, a resting state-based classifier of ASD was effective at differentiating SC (but not attention-deficit/hyperactivity disorder or depression) from controls (Yahata et al., 2016), suggesting a significant overlap in abnormal DMN patterns—involving also TPJ—between ASD and SC (Hyatt et al., 2020).

The posterior temporal clusters in which altered activity was found in autistic and schizophrenic patients are adjacent to the temporal regions, which, in healthy individuals, appear to support the graded transition between affective and cognitive mentalizing. While this proposal will require further supporting evidence, this overlap might underpin both affective and cognitive mentalizing deficits in autistic and schizophrenic patients. Unfortunately, the lack of studies investigating the two subcomponents of mentalizing does not allow to perform distinct meta-analyses specifically addressing affective or cognitive mentalizing in these populations.

Autistic patients additionally displayed decreased activity of the amygdala in association with tasks requiring an empathic processing. The involvement of this structure in ASD patients' social deficits was largely expected (e.g., Rausch et al., 2018), based on the notion that the amygdala underpins emotion-related social cognitive functions such as emotion recognition, socio-communicative perception and regulation of emotional responses (Inman et al., 2020). Increasing evidence indeed supports a system-level view of ASD patients' social deficits, whose severity reflects the degree of altered connectivity between the amygdala and other regions underpinning social communication and language, including MTG (Shen et al., 2016). Altogether, these data strengthen the view that ASD psychopathology might reflect the breakdown of crucial social cognitive functions such as mentalizing and empathy, related to functional (and possibly structural) alterations of some of their key neural correlates in the middle temporal cortex and amygdala (Rolls et al., 2020). Importantly, the presence of altered brain responses in association with both empathy and mentalizing in ASD is consistent with a model in which affective mentalizing depends on empathic ability (Shamay-Tsoory et al., 2010). Indeed, this model proposed that empathy supports affective mentalizing and, consequentially, an empathy deficit should be reflected also in affective mentalizing abnormalities. Unfortunately, due to the lack of studies on mentalizing in autistic population and schizophrenic patients, we could not implement two separate meta-analyses for affective and cognitive mentalizing.

#### 4.4 | Limitations

The present findings should be considered in the light of some limitations. First, in the meta-analysis on mentalizing in HC versus ASD, we included only 15 studies, against the suggested minimum number of 17 studies (Muller et al., 2018). While other meta-analyses on the same topic have included a similar number of studies (e.g., Dijkstra et al., 2020; Kim, Cunnington, & Kirby, 2020), this numerosity limits the generalizability of our findings. Moreover, participants' age was not a selection criterion for the studies comparing healthy participants

with autistic and schizophrenic patients. Although age-related parameters such as mean or range are typically not used to select studies for meta-analyses on clinical populations (e.g., Peng et al., 2020; Vucurovic et al., 2020), and social cognitive deficits have been reported regardless of age both in SC (Tordjman et al., 2019) and autism (Moody & Laugeson, 2020), the presence of differently aged populations might represent a possible confounding variable which future studies should control for. Finally, with the growth of the relevant literature, future studies might address possible specific alterations of brain activity associated with affective versus cognitive mentalizing in autism and SC. Only studying empathy, cognitive and affective mentalizing is possible to empirically confirm theoretical model on the relationship between these three socio-psychological constructs.

#### 4.5 | Conclusions and future directions

This quantitative meta-analysis of previously published fMRI data provides novel evidence on the neural bases of empathy, affective mentalizing and cognitive mentalizing, which might help refining the classification and neural characterization of these crucial building blocks of social communication (Cerniglia et al., 2019). The well-known ambiguity comes from the definition of cognitive versus affective subcomponents of ToM and empathy. Shamay-Tsoory is the first author who tried to clarify the situation, elaborating a model in which a specific role was defined for all of the components and our results confirm, at the neuroanatomical level, this proposals, according to which affective mentalizing builds on cognitive mentalizing and empathic skills (Shamay-Tsoory et al., 2010). This process might involve the contribution of adjacent regions underlying these functions in the posterior temporal, medial frontal, and inferior frontal cortex, some of which were additionally found to display altered brain activity in schizophrenic and/or ASD patients. While no empathy-related changes of brain activity were found in SC, the present evidence of altered ToM-related activity in the left posterior MTG/TPJ in both SC and ASD, and of empathy-related activity of the amygdala in ASD, paves the way for further studies addressing the neural bases of impaired social cognition and communication in these disorders. These results might also inform the design of rehabilitation interventions tailored on specific facets of social cognitive and communication skills which appear to be selectively impaired in different conditions, and of innovative treatment protocols targeting their specific neural correlates through neuromodulation (Davey et al., 2015; Donaldson, Rinehart, & Enticott, 2015).

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#### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

#### DATA AVAILABILITY STATEMENT

Data of this study are available from the corresponding author upon request.

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#### SUPPORTING INFORMATION

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