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Developing an intricate social brain

functional and structural correlates of socioemotional skills and their association with mental well-being

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Réka Borbás

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Prof. Dr. Dr. Christina Stadler
Prof. Dr. Dominique de Quervain
Prof. Dr. Nora Maria Raschle

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Prof. Dr. Jens Gaab

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Abstract

Socioemotional skills encompass a large set of abilities, which develop from early on and continue to being fine-tuned until late adulthood. The mastery of socioemotional abilities is associated with better social bonds and general psychological well-being in everyday life. Furthermore, it may also play an important role during challenging life circumstances. The fundamentals of mentalizing, the ability of perspective-taking, are acquired in early childhood laying the foundation for the development of more complex social skills across life. The ability to infer mental states aids interpersonal relations and is commonly considered beneficial. However, overly high, or low levels of mentalizing might lead to disturbances in social interactions or elevated stress. The neurobiological foundation for mentalizing has been well studied in adults, however evidence in developmental groups is still lagging behind, despite considerable advances in pediatric neuroimaging over recent years.

The main aim of this thesis was to summarize existing knowledge and generate new evidence on the development of the neural correlates for mentalizing. Furthermore, links between the neural correlates of socioemotional processing (i.e., mentalizing or emotion regulation) and psychosocial functioning are investigated. To achieve these goals, we first conducted a meta-analysis synthesizing theory of mind-related neural findings in children and adolescents comparing them to adult findings. Furthermore, we developed and validated a novel cartoon story-based theory of mind functional magnetic resonance imaging task feasible for young children. Finally, the onset of Covid-19 was recognized as a possibly impactful adverse global experience, allowing for the investigation of socioemotional and psychological well-being during challenging life circumstances. Neural correlates of mentalizing and emotion regulation skills were investigated in relation to mental health outcomes during the Covid-19 pandemic.

Within this thesis I first present meta-analytic evidence for an early development of the mentalizing network. Large correspondence of child, adolescent, and adult neural findings exist (as reflected by activation in temporoparietal junction, precuneus and middle medial prefrontal cortex across all age groups) but continuous change is observed across age, including more extensive activation pattern with increased age. Secondly, we developed a novel cognitive and affective theory of mind cartoon task (CAToon), which was evaluated behaviorally as well as through fMRI in children and adults. Our findings warrant future use of the task in developmental neuroimaging studies of mentalizing. Third, during stressful life circumstances, here associated with the Covid-19 pandemic, variations in adults' and children's mental health are observed. And finally, brain structure (i.e., emotion regulatory areas) and function (i.e., neural activation elicited during mentalizing) measured prior to the pandemic was linked to variables of psychosocial functioning in children and adults (e.g., fears about contamination or caregiving burden, anxiety, or depression).

In summary, my thesis I provides novel neuroimaging evidence that describes the development of socioemotional skills across childhood and adulthood and present selected examples of the association of socioemotional processes with mental well-being. In the future, neurodevelopmental studies assessing socioemotional skills and psychosocial functioning could profit from longitudinal approaches and the inclusion of a combination of neurophysiological and behavioral measures from an early age.

1. Introduction

1.1. Socioemotional Development

Humans are inherently social beings, and their well-being across the lifespan greatly relies on their social contexts (Aronson, 2003). The high degree of reliance starts already at birth, as human newborns are exceedingly dependent on the caregiving provided by the ones surrounding them. Such a dependence is partly due to the relatively underdeveloped brain at birth and a prolonged neurodevelopmental phase compared to other species (Atzil et al., 2018; Johnson, 2001). Hence, humans care for their young over a remarkably long period of time compared to our closest primate relatives (Gopnik et al., 2017; Hawkes & Coxworth, 2013; Hill & Kaplan, 1999; Uomini et al., 2020). This high degree of dependence and extended developmental phase leaves humans with a large time window for learning and adapting and establishes the important role of interpersonal experiences (Johnson, 2001; Uomini et al., 2020; Yaniv et al., 2021).

Starting already in the mother's womb there is a constant exchange of social information. During infancy and early childhood parents or primary caregivers are the main architects of the infant's surroundings, serving as first models of social behavior. Even though this exchange is lopsided in the initial phases of development (i.e., primary caregivers assume a more active role than their offspring, regulating their allostasis unilaterally (Atzil et al., 2018)), infants acquire the fundamentals of human interaction already in these early stages. For example, the mere exposure to post-partum skin-to-skin contact shapes later mother-child interaction and consequent neural empathy in adulthood (Yaniv et al., 2021), and breastfeeding positively influences later problem solving and personal-social skills, including interaction with others and self-care (McCrory & Murray, 2013). More generally, through the primary caregiver's regulation of the infant's allostasis the child acquires the ability to synchronize, which underlies the capacity to tune in to others laying the basis of better interactions and self-regulation when the infant becomes older (Atzil et al., 2018).

Later, in addition to such basic forms of physical interactions, more complex exchanges start to take place. The development of the child's attention, memory and executive functions allows for new ways of gathering and processing information. A well-researched way of learning is observational learning, in which initially the primary caregivers and later the extended social circle serve as models of behavior, values, and attitudes, enabling the learning and reproduction of these (Bandura, 2008). For example, verbal interaction, such as an elevated use of language including emotional and mental states in parents, may also serve as a primer for later prosocial behavior in their children (Drummond et al., 2014). More broadly, early interactions greatly shape later social abilities on a behavioral and neural level (Atzil et al., 2018; Drummond et al., 2014; Yaniv et al., 2021).

As children enter the educational system, their social world expands. Adults outside of the family and peers become increasingly influential in shaping the child's socioemotional development (Arndt, 2012). Social abilities learned during the early years play a vital role within this environment, as poor skills may lead to lower friendship quality and victimization (Crawford & Manassis, 2011). Forming high-quality bonds with peers is not only connected to general well-being (Demir et al., 2012) but such bonds also serve as defining settings promoting further refinement of social development (Berndt, 2002; Glick & Rose, 2011). Moreover, friendships have a mediating role between social skills and happiness (Demir et al., 2012). Having a great mastery of social skills is therefore not only directly beneficial for an individual's relationships and social interactions, but it also affects general psychological well-being significantly (Segrin & Taylor, 2007). Thus, social development during early years has far-reaching consequences and needs to receive attention in educational and therapeutic settings.

1.2. Theory of mind

Theory of mind (ToM) is a fundamental cognitive ability serving as a scaffolding for many later developing social skills. ToM refers to the ability of making inferences about one's own and others' mental states, including feelings, thoughts, beliefs, desires, or intentions (Frith & Frith, 2005; Saxe, 2006). The term 'mentalizing' was introduced by pioneering ToM researcher Uta Frith to express the action of engaging in the use of theory of mind (Frith, 1989), and has been in use ever since. The knowledge we gain from mentalizing can be used to better understand behaviors and actions of others, but also to grasp how others might perceive us. Conceptually, the literature differentiates between *affective* and *cognitive* mentalizing (Sebastian et al., 2012; Shamay-Tsoory et al., 2010) depending on the type of inference, which is made, i.e., understanding others' affective states versus understanding their intentions and beliefs.

The study of ToM originates from behavioral animal research (Premack & Woodruff, 1978) discovering a chimpanzee's ability to make correct inferences about a human actor's intention in several problematic scenarios shown to her. Soon, the first studies in humans ensued, setting out to discover at what age children developed a theory of mind (Wimmer & Perner, 1983). Initial studies relied on so-called false belief tasks, which test whether a child can understand that another person's knowledge differs from their own, influencing their actions (e.g., Maxi task or Sally-Anne task (Baron-Cohen et al., 1985; Wimmer & Perner, 1983)). A review of the first two decades of developmental studies reflects that children acquire ToM around the age of 4 to 5 years (Wellman et al., 2001). However, a shift in the experimental design and paradigms used in behavioral studies (e.g., nonverbal tasks assessing infant's looking times) revealed a much earlier presence of mental state attribution in infants of 13-15 months (Onishi & Baillargeon, 2005; Surian et al., 2007).

1.2.1. Neural bases of mentalizing

Behavioral reports on mentalizing are complemented by investigations of the neural underpinnings of this complex social skill. First studies exploring the neural correlates of mentalizing used positron emission tomography in healthy adults (Fletcher et al., 1995; Goel et al., 1995) later expanding to include clinical populations (e.g., autism spectrum disorder (Happe et al., 1996; Takeuchi et al., 2002)). A comprehensive collection of neuroimaging studies as well as meta-analyses deriving from the past three decades describe a robust pattern of activation during theory of mind tasks. Brain areas consistently detected in the *'mentalizing network'* include the precuneus, bilateral temporoparietal junction, medial prefrontal cortex, inferior frontal gyrus, precentral gyrus, anterior cingulate cortex, temporal poles, middle temporal gyrus and superior temporal sulcus (Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle & Baetens, 2009). It is important to note, that the majority of early mentalizing-related neuroimaging findings are based on adults, and no meta-analytic study to date has investigated theory of mind-based neural activation in the developing brain, though some studies draw a comparison between adult and child theory of mind processing (Kobayashi et al., 2007; Richardson et al., 2018).

The relative scarcity of pediatric studies in neuroimaging can be potentially explained by the unique challenges researchers working with developmental groups face (Raschle et al., 2012; Thieba et al., 2018). Firstly, recruitment is more challenging in the younger age ranges. Parents can be anxious about letting their children participate, especially if the technological tools are unfamiliar or linked to unpleasant experiences. Secondly, movement during a magnetic resonance imaging (MRI) session occurs more frequently in pediatric populations, causing data loss or artefacts (Poldrack et al., 2002; Power et al., 2012). The above difficulties can be minimized by employing a proper training protocol (e.g., reducing anxiety by providing easy-to-understand information, and motivating the child to stay still in a playful way), or by post-hoc correction methods accounting for movement. A third aspect to consider is the task used to evoke neural activation during a functional neuroimaging session. Pediatric studies often employ stimulus material developed and validated in adults. Accordingly, initial mentalizing-related neuroimaging studies in children (Gweon et al., 2012; Kobayashi et al., 2006; Ohnishi et al., 2004) were using paradigms borrowed from adult studies with slight changes. Such a task can be dull for children, resulting in decreased motivation which in turn significantly affects task performance (Renninger & Hidi, 2015). Therefore, paradigms that were designed and tested with developmental groups in mind are needed in the field of pediatric neuroimaging. In recent years there have been several studies using relatively kid-friendly naturalistic viewing paradigms (passive video watching) including video clips of people (Hyde et al., 2018), Toy Story excerpts (Moraczewski et al., 2018), a Pixar short movie (Reher & Sohn, 2009; Richardson et al., 2018; Richardson & Saxe, 2020) or Sesame street clips (Cantlon & Li, 2013). These tasks work especially well in very young age ranges, as they do not require any explicit responses from the participants (often a hurdle when conduction research in infants), and the stimuli are inherently engaging for the targeted age group.

Neuroimaging studies investigating mentalizing in developmental groups, including fMRI, functional near infrared spectroscopy (fNIRS) and electroencephalogram (EEG), have been delivering evidence of early functional organization and specificity of the mentalizing network (Bowman et al., 2019; Gweon et al., 2012; Hyde et al., 2018; Richardson et al., 2018; Richardson & Saxe, 2020). The earliest presence of mentalizing-specific functional organization was observed in 7-month-old infants via fNIRS (Hyde et al., 2018), marked by the temporoparietal junction responding specifically to video clips of people holding false beliefs. Studies of passive cartoon movie watching within the fMRI further showcase evidence of a functionally distinct mentalizing network already in 3-year-old children (Richardson et al., 2018; Richardson & Saxe, 2020), even if the children consistently fail behavioral false belief tests. In addition, the time course of neural activation in the ToM network between adults and 3-year-olds is strongly correlated highlighting the early maturation of the mentalizing system (Richardson et al., 2018). Importantly, cross-sectional studies observing a broad age range (Gweon et al., 2012; Moraczewski et al., 2018; Richardson et al., 2018) but also longitudinal approaches (Richardson & Saxe, 2020) underline that although functional organization of the ToM network is present very early, the specificity of the involved areas improves with the progression of age in children. In summary, behavioral studies indicating an earlier presence of implicit mentalizing in infants (Onishi & Baillargeon, 2005; Southgate et al., 2007; Surian et al., 2007) are further complemented by novel developmental neuroimaging studies (Richardson et al., 2018; Richardson & Saxe, 2020) observing the early presence of mentalizing-related brain networks with further functional specialization (Gweon et al., 2012; Moraczewski et al., 2018; Richardson & Saxe, 2020) as children age.

1.2.2. The role of mentalizing and its effects on intra- and interpersonal factors

Impaired mentalizing has been observed in diverse clinical populations. More specifically, hypomentalization (a lower tendency to assume the perspective of others or oneself) has been associated with autism spectrum disorder (Frith, 2001), specific language impairment (Gillott et al., 2004), alexithymia (Moriguchi et al., 2006), and attention-deficit hyperactivity disorder (Uekermann et al., 2010). Hypermentalization (the propensity to overtake others' mental states) has been widely observed in patients with a diagnosis of borderline personality disorder (Bateman & Fonagy, 2006; Fonagy & Bateman, 2008; Sharp & Vanwoerden, 2015) and in some cases of social anxiety (Ballespí et al., 2019). Both under- and overmentalizing can be disadvantageous as they can lead to the neglect of vital social cues hindering successful social interaction (Frith, 2001) or to the overinterpretation of intent or affect that is not present (Ballespí et al., 2019).

In non-clinical populations a higher level of perspective-taking has been identified as a predictor of less behavioral problems in children (Wells et al., 2020), highlighting the benefits of adequate mentalizing. Furthermore, well-developed mentalizing skills can also be advantageous in mother-child relationships, as shown by better self-regulation in children whose mothers tend to mentalize more (Senehi et al., 2018) or report higher empathetic concern in relation to their child (Manczak et al., 2016). Self-mentalizing (understanding one's own mental states) can also be a protective factor in stressful situations, enabling better self-reflection, which promotes adequate coping behavior (Schwarzer et al., 2021). Notably, elevated caring, as displayed by an inclination to mentalize or empathize with others, can have negative consequences, as displayed e.g., by elevated levels of inflammation markers (Manczak et al., 2016) or higher stress markers during social stress (i.e., cortisol, heart rate reactivity; (Tollenaar & Overgaauw, 2020)). In summary, mentalizing is broadly considered beneficial for interpersonal relations (Caputi et al., 2012) and can serve as a protective factor as it allows us to tune into others and ourselves, however, in some contexts more mentalizing can be '*too much of a good thing',* causing a surplus of distress.

1.3. Covid-19: a natural experiment of mental health

As the last days of 2019 were coming to an end, a then unknown respiratory virus reared its head in the city of Wuhan, Hubei Province, China. The number of cases grew rapidly, and the World Health Organization declared the outbreak of this novel virus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a global pandemic on March 11, 2020 (CDC, 2021). Countries all over the world reacted with nation-wide lockdowns or restrictions, inflicting an unparalleled restructuring of everyday life on a global scale. Measures included stay-at-home orders, recommendations, or orders of working from home, school closures, closure of non-essential stores, and travel bans. Even though measures taken to lessen the spread of the virus and the collapse of the healthcare system were greatly heterogeneous across countries (Asongu et al., 2020), most of them limited peoples' lives in an unprecedented way. A prominent consequence of these limitations was social isolation (Hwang et al., 2020; Jurblum et al., 2020). A swift adjustment to new circumstances was inevitable, deeply affecting people's personal and professional lives with little to no time for preparation. In such a crisis, certainty and valid central information can be important stabilizing factors. Unfortunately, reports indicate highly contradicting information reaching people from different media outlets (Filkuková et al., 2021; Koffman et al., 2020), increasing fear and uncertainty. In summary, people were confronted with manifold challenges, i.e., financial, health, personal, professional, due to the direct and indirect effects of the Covid-19 outbreak. Facing such challenges requires the employment of diverging personal resources, including external ones, such as social support, but also internal ones, as for example coping mechanisms of the individual.

First evidence indicated an initial rise in mental health issues due to Covid-19 and related restrictions across the globe (Achterberg et al., 2021; Crescentini et al., 2020; de Quervain et al., 2020; Ettman et al., 2020; Kwong et al., 2021; Ozamiz-Etxebarria et al., 2020), though the extent of adverse effects can differ largely depending on gender, relationship and employment status, financial security or previous mental and physical health (Achterberg et al., 2021; Kuhn et al., 2021; Kwong et al., 2021). Notably, over the course of the past one and a half years, studies observed many possible trajectories during the pandemic, including worsening, plateauing, ameliorating mental health often displaying non-linear trends over longer periods of time (Achterberg et al., 2021; Kuhn et al., 2021; Loosen et al., 2021; O'Connor et al., 2021; Prati & Mancini, 2021; Robinson & Daly, 2021; Salfi et al., 2021). Crises, independently of their nature, interrupt the normal way of life and can significantly alter development, placing families and especially children in a highly vulnerable position (Ager et al., 2010). Overall, although the Covid-19 pandemic poses unprecedented challenges for many, it seems that there is great variation in the individual responses to it. Therefore, an important area of investigation entails the identification of intrapersonal or contextual characteristics serving as risk or resilience factors during a pandemic.

1.4. Gaps in knowledge

In the previous two decades behavioral theory of mind research has been complemented by numerous neuroimaging studies in healthy and clinical populations, enriching the field. Nevertheless, neural evidence and interpretation still strongly still relies on adult findings, as indicated by several meta-analyses present in adult groups (Molenberghs et al., 2016; Schurz et al., 2013; Van Overwalle & Baetens, 2009; van Veluw & Chance, 2014), but none with a specific focus on children to date. As a consequence of technological advances and more adequate protocols, studies in developmental groups have multiplied in recent years, making the summary and comparison of findings an interesting and timely objective. Therefore, the first aim of this thesis entails the compilation of all eligible mentalizing studies using functional magnetic resonance imaging in developmental groups by conducting a systemic literature review followed by a coordinate-based meta-analysis. In **Study I** we used activation likelihood estimation (ALE) meta-analyses, performed via GingerALE (Eickhoff et al., 2009) to summarize and contrast neuroimaging evidence in developmental groups and adults during mentalizing analyses to inform about brain regions consistently or differentially engaged across age categories. Specifically, **Study I** investigated shared and distinct neural activation in these age groups.

A described above, studies of the mentalizing neural network are becoming more numerous in developmental groups. Many are employing paradigms borrowed from adult studies, allowing for a controlled design, and recording behavioral responses inside the scanner. This limits the possible age of participants, because of task complexity. Other studies are choosing a more child-friendly and entertaining approach by showing animation movies to the participants requiring no response, allowing for the investigation of implicit mentalizing and results from a broader age-range, however with no in-scanner response from the participants.

For aim 2 successful and validated features of past theory of mind tasks were combined to create a novel cognitive and affective Theory of Mind fMRI task, suitable for young children and families. **Study II** therefore describes the creation and validation of a neuroimaging mentalizing task designed for all age groups.

The Covid-19 pandemic occurred in the midst of my doctoral research studies. The pandemic did not only change our world as we knew it, but likewise impacted many ongoing research endeavors. Given my focus on the neural and behavioral correlates of socioemotional development in children and mother-child dyads, the pandemic posed an unexpected natural experiment. Due to its recent occurrence little was known about the mental health consequences of Covid-19 and related restrictions. Therefore, aim 3 of my research was the examination of short-term effects of the Covid-19-outbreak on mental health and their association with neural correlates of mentalizing measured prior to the pandemic. More specifically, participants that were already enrolled in ongoing studies were invited to continue a questionnaire-based online investigation on mental well-being during the first months following nationwide restrictions in Switzerland. While we did not intend to run a Swiss-wide survey on mental health, our aim (**Study III**) was to implement repeated measures assessments and examine the well-being of children, young adults and parents that had been well-characterized through behavioral and neural data prior to Covid-19 onset. Aim 4 (**Study IV**) entailed the investigation of later effects of Covid-19 and related restrictions in the same group of participants by adding an assessment nine months after the start of the first restrictions in Switzerland. Neural and behavioral markers of emotion-regulation were tested as potential risk or resilience factors.

1.5. Aims

(1) Review and compare the current knowledge on the neural correlates of mentalizing in children, adolescents, and adults through meta-analytic methods.

(a) Conduct a systematic literature review of mentalizing-related neuroimaging findings in children, adolescents, and adults.

(b) Perform meta-analyses to identify commonly recruited areas during mentalizing in each age group.

(c) Identify shared and distinct activation in children, adolescents, and adults, to uncover possible age effects.

(2) Creation of a novel cognitive and affective theory of mind fMRI task suitable for young children and all age groups.

(a) Based on the literature research conducted in **Study I**, identify successful and relevant features of previous theory of mind tasks and implement these in the development of a novel neuroimaging paradigm suitable for young children within an fMRI environment.

(b) Behavioral task evaluation in a broad age range of children and neural task evaluation in children and adults.

(3) Investigation of the short-term impact of Covid-19 on children and adults, including behavioral evidence and neural precursors.

(a) Investigation of the effects of Covid-19 and associated restrictions on child and adult well-being as measured repeatedly during the first months after Covid-19 onset.

(b) Assessment of the association between mental well-being (e.g., anxiety, depression, caregiver burden) in mothers and children's emotional and behavioral problems or mood.

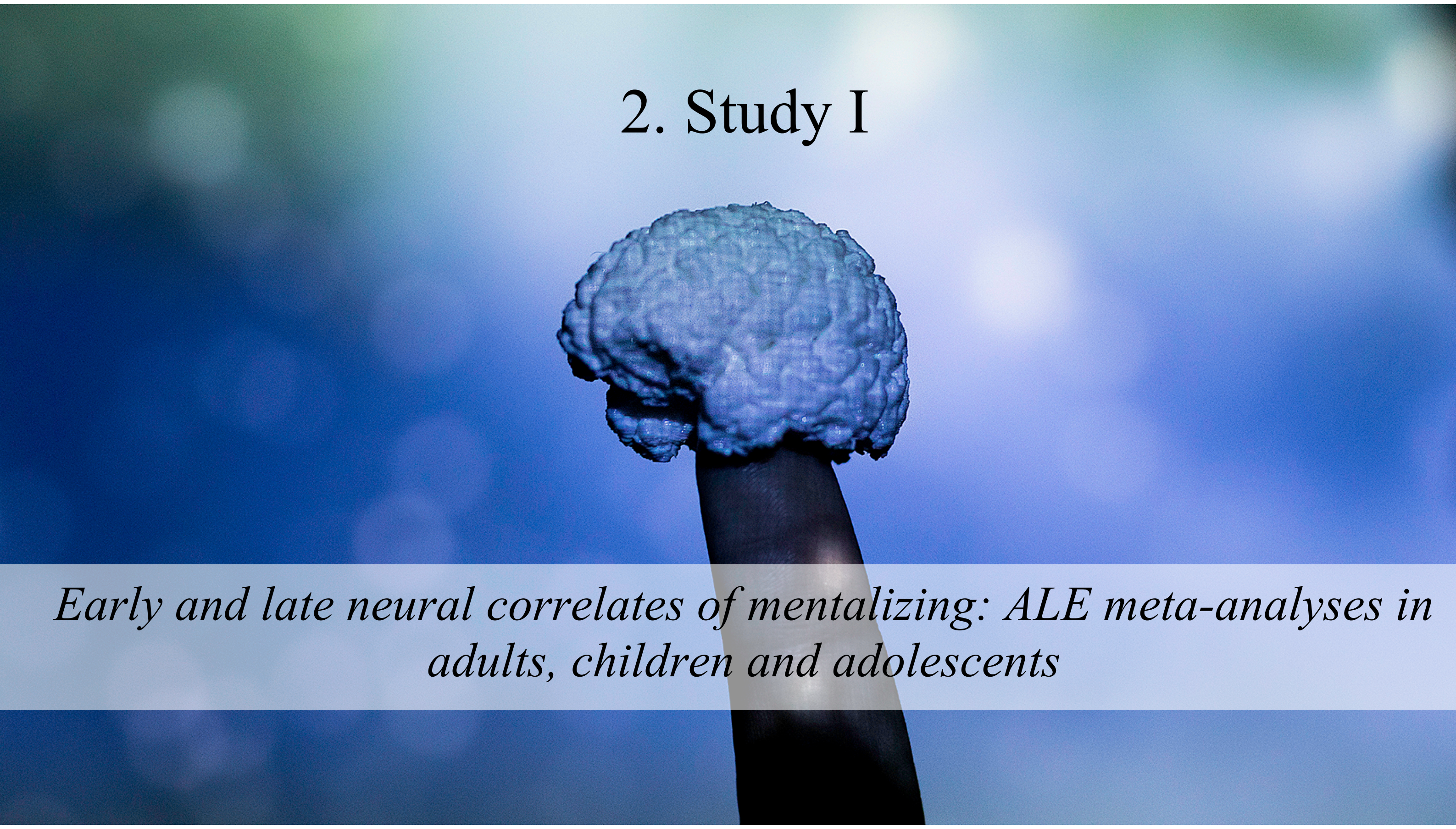
(c) Examination of the association between the neural correlates of mentalizing as measured prior to Covid-19 and later development of fear of contamination and illnesses in all participants, or caregiver burden in mothers.

(4) Investigation of the long-term effect of Covid-19 on mental well-being and assessment of the relationship of structural brain measures and emotion regulation strategy use and mental health.

(a) Description of changes in mental health across the first ten months after Covid-19 onset in adults.

(b) Investigation of different cognitive emotion regulation strategies and their effect on mental health.

(c) Testing whether emotion regulatory brain structure measured prior to Covid-19 onset is associated with mental well-being during the pandemic and whether this association is mediated by the use of certain emotion regulation strategies.



2. Study I

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

Lynn V. Fehlbaum[1,2], **Réka Borbás[1,2]**, Katharina Paul[2], Simon B. Eickhoff[3,4], Nora M. Raschle[1,2,5]

[1] Jacobs Center for Productive Youth Development at the University of Zurich, Zurich, Switzerland

[2] Department of Child and Adolescent Psychiatry, University of Basel, Psychiatric University Hospital, Basel, Switzerland

[3] Institute of Systems Neuroscience, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

[4] Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7), Research Centre Jülich, Jülich, Germany

[5] Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland

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Abstract

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

Keywords: mentalizing, functional neuroimaging, development, children, adults

1. Introduction

A fundamental premise of our everyday social life is the ability to understand and acknowledge the emotions and intentions of people around us. The constantobservation, decoding and understanding of the mental states of ourselves and others is reflected in our mentalizing skills and enabled by our Theory of Mind (Frith & Frith, 2007). Mentalizing skills have shown to be positively associated with healthy social functioning (Slaughter et al., 2015). Atypical mentalizing skills, however, have been described for several neurodevelopmental psychiatric disorders, including autism spectrum disorders, conduct disorder, depression, schizophrenia or borderline traits (Baron-Cohen et al., 1997; Kerr et al., 2003; Kronbichler et al., 2017; Moran et al., 2011; Sharp, 2008; Sharp et al., 2011; Zobel et al., 2010). Amongst these, hypermentalizing (e.g., borderline personality disorder), reduced mentalizing (e.g., psychopathy) or altered mentalizing skills (e.g., conduct disorder) have been reported (Blair et al., 2004; Sharp et al., 2011). Given their daily critical role and importance for clinical diagnostics, mentalizing concepts have been key targets of different therapy settings (Björgvinsson & Hart, 2006; Fonagy & Allison, 2014; Fonagy et al., 2017).

The foundation for mature mentalizing skills is laid early in life (Baillargeon et al., 2010). For example, mothers' use of mental state language with their six-months-old infants has been shown to predict children's later Theory of Mind performance (Meins et al., 2003; Meins et al., 2002). Similarly, false belief tasks during which basic inferences are used to predict other people's intentions can already be employed in infancy (Knudsen & Liszkowski, 2012). Major conceptual improvements in mentalizing skills are suggested to occur around 3 to 6 years of age (Wellman et al., 2001). However, mentalizing skills continue to mature throughout childhood and adolescence (Blakemore, 2008; Crone & Dahl, 2012; Crone & Steinbeis, 2017). Across age and skill levels, individuals learn to mentalize in a flexible and adaptive manner, allowing the interpretation of increasingly complex social situations (Korkmaz, 2011).

The neural correlates of mentalizing in adulthood have been studied through various functional magnetic resonance imaging (fMRI) paradigms. Common implementations of mentalizing in fMRI paradigms include the false belief task (Mitchell, 2007; Tamnes et al., 2010), Frith–Happé animations (Gobbini et al., 2007; Moriguchi et al., 2006) or the Reading the Mind in the Eyes Test (Gallagher et al., 2000; Mascaro et al., 2013). Other studies have implemented paradigms more broadly related to mentalizing processes, for example through the study of self-referential knowledge (e.g., (Ochsner et al., 2005; Pfeifer et al., 2007)) or by motivation or mental state attributions underlying body movements (Spunt & Lieberman, 2012; Wurm & Schubotz, 2018). Overall, past evidence has identified core regions of the social brain during mentalizing in adults, including medial prefrontal cortex, bilateral temporoparietal junction, precuneus, inferior frontal gyri and the temporal lobes (Kliemann & Adolphs, 2018). More precisely, most studies have revealed consistent increases in brain activation during mentalizing in the medial prefrontal cortex and bilateral temporoparietal junction (summarized by meta-analyses: (Mar, 2011; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle, 2009; van Veluw & Chance, 2014)). Additionally, areas including the posterior superior temporal sulci and gyri, temporal poles, precuneus and inferior frontal gyri (Mar, 2011; Molenberghs et al., 2016), as well as anterior (Molenberghs et al., 2016) and posterior (Mar, 2011) cingulate cortices and middle temporal gyri (van Veluw & Chance, 2014) were identified by some, but not all studies. Differences in study reports have been suggested to result from variations in task choice which may require further cognitive processes (Mar, 2011; Molenberghs et al., 2016; van Veluw & Chance, 2014). Furthermore, in adults, connectivity between mentalizing regions (including temporoparietal junction, precuneus and medial prefrontal cortex) and insula, pre- and postcentral gyri and ventrolateral prefrontal cortex has been reported (Atique et al., 2011; Burnett & Blakemore, 2009; Lombardo et al., 2010; Schuwerk et al., 2014).

fMRI studies of mentalizing in children are more scarce compared to work conducted in adults. However, in line with technical and practical advances (Bednarz & Kana, 2018; Raschle et al., 2012; Vijayakumar et al., 2018), knowledge on early neural correlates of mentalizing continues to accumulate. Existing developmental studies of mentalizing indicate an early specialization and potential continuous engagement of some core regions associated with mentalizing in children starting around three (Richardson et al., 2018; Richardson & Saxe, 2020) to five years of age (Gweon et al., 2012), for regions including medial prefrontal cortex, temporoparietal junction and precuneus. Similarly, activation increases in regions including temporoparietal junction, precuneus, inferior parietal lobe and superior temporal sulci were detected in children aged eight to 13 years (e.g., (Kobayashi et al., 2007; Moriguchi et al., 2007; Mukerji et al., 2019; Yokota et al., 2013)). To date only few studies have directly investigated developmental effects for the neural correlates of mentalizing using longitudinal designs (Overgaauw et al., 2015; Schulte-Rüther et al., 2012). Such studies have detected stable activation in core regions for mentalizing, including medial prefrontal cortex, temporoparietal cortex, precuneus and superior/middle temporal and fusiform gyri in adolescents aged 12–18 (Schulte-Rüther et al.,

2012) and in right superior temporal sulcus and inferior frontal gyrus adolescents aged 12–19 (Overgaauw et al., 2015). Overgaauw and collegaues (2015) additionally report non-linear developmental trajectories for dorsal medial prefrontal cortex and linear decreases for right inferior frontal gyrus across age.

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

Here we aimed to compile and compare existing knowledge on the neural correlates of mentalizing in children, adolescents and adults. Our main aims were to (I) perform a coordinate-based meta-analysis integrating data on neural activation and functional connectivity patterns during mentalizing in adults, (II) compute a coordinate-based meta-analysis to integrate existing data on neural activation during mentalizing in children/adolescents and (III) run a conjunction analysis to reveal common brain regions activated by adults and children/adolescents during mentalizing. Additionally, a contrast analysis in children/adolescents versus adults will be computed to detect distinct brain activation during mentalizing. Finally, (IV) follow-up analyses comparing children and adolescents allow for a first indication of neural patterns observed in younger children as compared to adolescents. Based on previous studies we hypothesized mentalizing in adults to be associated with activation in medial prefrontal cortex, temporoparietal junction, precuneus, inferior frontal gyri and temporal cortex (Mar, 2011; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle, 2009; van Veluw & Chance, 2014). Moreover, functional connectivity between mentalizing regions (temporoparietal junction/posterior superior frontal sulcus, medial prefrontal cortex), and areas engaged during lower-level processes (Atique et al., 2011; Burnett & Blakemore, 2009; Lombardo et al., 2010; Schuwerk et al., 2014) were expected. For children/adolescents, a similar but still developing activation pattern is hypothesized, reflected by the activation of some, but not all, areas reported in adults (e.g., engagement of medial prefrontal cortex, but only emerging activation of the temporoparietal junction/superior temporal cortex; (Blakemore, 2008, 2012a, 2012b; Crone & Dahl, 2012)).

2. Methods

2.1. Literature search and study selection

We conducted systematic and standardized meta-analyses corresponding to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the revised Quality Of Reporting Of Meta-analyses statement (Moher et al., 2009). Our main literature search was conducted through PubMed and included the keywords “fMRI Theory of Mind” with and without the restriction to “children” and/or “adolescents” (search date in adults: 04.12.2018, in children/adolescents: 01.11.2019). Additionally, the reference lists of past meta-analyses and reviews investigating mentalizing were screened to identify any reports previously not detected (for details see PRISMA flow diagram, **Supplementary Information 1**). Inclusion criteria for studies entering our meta-analyses were: whole-brain findings, coordinates provided in standard space (i.e., Talairach & Tournoux or Montreal Neurological Institute space), contrasts targeting mentalizing, English publications. Studies based on region of interest (ROI) analyses or non-fMRI studies (e.g., electroencephalography, structural neuroimaging) and studies only yielding hypoactivations were excluded. The activation likelihood estimation methodology applied here does not allow inclusion of null findings and does not account for differences in thresholding of the studies entering the meta-analyses. A main goal of the present study was the investigation of brain activity related to mentalizing in adults and the comparison of these findings to evidence deriving from studies in children/adolescents. Studies that report brain activity deriving from mixed groups of adolescents and adults (without separate coordinates for adults and children/adolescents) were not included. Data from clinical research studies were only included for the healthy subgroups (i.e., coordinates on healthy control groups or main effects, representing brain activation equal to the clinical and control groups).

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

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

First author, year	N	Task type	First author, year	N	Task type	First author, year	N	Task type
Gallagher*, 2000	6	ToM cartoon, ToM reading	**Kim*, 2005**	14	Matching faces with situation	**Todorov*, 2007**	9	Matching faces with behavior
Russell*, 2000	7	Reading the Mind in the Eyes	**Ochsner*, 2005**	16	Self-referential thinking (reading)	**Wakusawa*, 2007**	31	Irony/metaphor
Vogeley*, 2001	8	ToM reading	**Aichhorn*, 2006**	21	Visual perspective taking	**Young*, 2007**	27	False belief
Ferstl*, 2002	9	ToM reading	**Elliott*, 2006**	12	Reward processing	**Abraham*, 2008**	17	ToM reading
Martin*, 2003	12	Frith-Happé	**Fukui*, 2006**	16	Reward processing	**Brüne*, 2008**	13	ToM cartoon
Saxe*, 2003	25	False belief	**Fukui*, 2006**	16	Reward processing	**Hooker*, 2008**	20	False belief
Decety*, 2004	12	Computer/human interaction	**Marjoram*, 2006**	13	Humor, false belief	**Kédia*, 2008**	29	Pain/harm in others
Gallagher*, 2004	13	Expressive gestures	**Moriguchi*, 2006**	38	Frith-Happé	**Kliemann*, 2008**	26	False belief
German*, 2004	16	Pretended/real actions	**Saxe*, 2006**	12	False belief	**Kobayashi*, 2008**	16	False belief
Gobbini*, 2004	10	Face familiarity	**Saxe*, 2006**	12	False belief	**Krach*, 2008**	20	Prisoner's dilemma
Grèzes*, 2004	6	False belief	**Spiers*, 2006**	20	ToM cartoon	**Malhi*, 2008**	20	Frith-Happé
Leibenluft*, 2004	7	Own/others' children face processing	**Uchiyama*, 2006**	20	Sarcasm	**Mason*, 2008**	18	ToM reading
Platek*, 2004	5	Reading the Mind in the Eyes	**Völlm*, 2006**	13	ToM cartoon	**Rilling*, 2008**	20	Prisoner's dilemma
Rilling*, 2004	19	Prisoner's dilemma	**Cheng*, 2007**	14	Pain/harm in others	**Samson*, 2008**	17	Humor
Seger*, 2004	12	Food preferences of others	**Gilbert*, 2007**	16	Evaluation of helpfulness (reading)	**Sommer*, 2008**	18	Emotion attribution
Walter*, 2004	13	ToM cartoon	**Gobbini*, 2007**	24	Frith-Happé, false belief	**Vanderwal*, 2008**	17	Frith-Happé
Walter*, 2004	12	ToM cartoon	**Kobayashi*, 2007**	24	False belief	**Young*, 2008**	14	False belief
Bhatt*, 2005	16	Self-referential thinking (reading)	**Mitchell, 2007**	20	False belief	**Aichhorn*, 2009**	21	False belief
den Ouden*, 2005	11	ToM reading	**Schulte-Rüther*, 2007**	26	Emotional state evaluation (images)	**Assaf*, 2009**	19	Computer/human interaction
Harris*, 2005	12	ToM reading	**Sommer*, 2007**	16	False belief	**Bahnemann*, 2009**	25	Cartoon ToM
First author, year	**N**	**Task type**	**First author, year**	**N**	**Task type**	**First author, year**	**N**	**Task type**

Jenkins*, 2009	15	False belief	**Rapp*, 2010**	15	Irony	**Spunt*, 2011**	15	Action identification (images)
Kircher*, 2009	12	Prisoner's dilemma	**Ross*, 2010**	15	Frith-Happé	**van der Meer*, 2011**	19	False belief
Krach*, 2009	24	Prisoner's dilemma	**Shibata*, 2010**	13	Irony	**Walter*, 2011**	109	ToM cartoon
Mano*, 2009	18	ToM reading	**Sommer*, 2010**	12	False belief	**Young*, 2011**	17	False belief
Otsuka*, 2009	24	ToM reading	**Sommer*, 2010**	14	ToM cartoon	**Becchio*, 2012**	16	Reach-to-grasp action movies
Sripada*, 2009	26	Computer/human interaction	**Wolf*, 2010**	18	ToM cartoon/movie	**Canessa*, 2012**	27	ToM images
Walter* 2009	12	ToM cartoon	**Yoshida*, 2010**	12	Predict peer strategy during game	**Chaminade*, 2012**	18	Computer/human interaction
Young*, 2009	28	False belief	**Young*, 2010**	17	False belief	**Cheung*, 2012**	20	False belief
Abraham*, 2010	22	False belief	**Zaitchik*, 2010**	15	False belief	**Das*, 2012**	22	Frith-Happé
Adams*, 2010	28	Reading the Mind in the Eyes	**Centelles*, 2011**	14	ToM motion movie	**de Achával*, 2012**	14	Reading the Mind in the Eyes
Castelli*, 2010	24	Reading the Mind in the Eyes	**Dodell-Feder*, 2011**	62	False belief	**Döhnel*, 2012**	18	False belief
Focquaert*, 2010	24	Reading the Mind in the Eyes	**Koelkebeck*, 2011**	15	Frith-Happé	**Hartwright*, 2012**	19	False belief
Hooker*, 2010	15	ToM cartoon	**Lee*, 2011**	13	False belief	**Kestemont*, 2012**	34	ToM reading
Jimura*, 2010	34	False belief	**Liew*, 2011**	18	Interpretation of others' gestures	**Mascaro*, 2012**	21	Reading the Mind in the Eyes
Kim*, 2010	24	Matching faces with situation	**Ma*, 2011**	30	ToM reading	**Mier*, 2012**	13	ToM reading/faces
Lombardo*, 2010	33	ToM reading	**Ma*, 2011**	15	ToM reading	**Moran*, 2012**	128	Frith-Happé, moral judgement, false belief
Marsh*, 2010	24	Action identification (reading)	**Mason*, 2011**	10	ToM reading			
Mier*, 2010	16	ToM reading/faces	**McAdams*, 2011**	17	Frith-Happé	**Rabin*, 2012**	18	Images of others'/own events
Mier*, 2010	40	ToM reading/faces	**Otsuka*, 2011**	22	ToM reading	**Roser*, 2012**	14	False belief
Modinos*, 2010	36	ToM cartoon	**Polosan*, 2011**	14	Computer/human interaction	**Spotorno*, 2012**	20	Irony
Murphy*, 2010	10	Evaluation of others' attributes	**Rothmayr*, 2011**	12	False belief	**Spunt*, 2012a**	21	Action identification (images)
Pincus*, 2010	9	Reading the Mind in the Eyes	**Schnell*, 2011**	21	ToM cartoon	**Spunt*, 2012b**	22	Action identification (images)
Rabin*, 2010	18	Images of others'/own events	**Shibata*, 2011**	15	Indirect speech	**Uchiyama*, 2012**	20	Sarcasm/metaphors
First author, year	**N**	**Task type**	**First author, year**	**N**	**Task type**	**First author, year**	**N**	**Task type**
Veroude*, 2012	25	False belief	**Spunt*, 2014**	29	Action identification (images)	**van Ackeren*, 2016**	25	Indirect speech processing

Bodden*, 2013	30	False belief	**Van Hoeck*, 2014**	19	ToM reading	**Bravo*, 2017**	14	Auditory ToM
Contreras*, 2013	36	ToM reading, false belief	**Alderson-Day*, 2015**	19	False belief	**Desmet*, 2017**	17	Frith-Happé
Corradi-Dell'Acqua*, 2013	46	False belief	**Frank*, 2015**	34	False belief	**Döhnel*, 2017**	22	False belief
Dufour*, 2013	27	False belief	**Hartwright*, 2015**	21	False belief	**Eddy*, 2017**	25	False belief
Hervé*, 2013	42	ToM reading	**Kandylaki*, 2015**	20	False belief	**Feng*, 2017**	23	Indirect replies
Kullman*, 2013	18	Reading the Mind in the Eyes	**Kanske*, 2015**	25	ToM reading/faces	**Lewis*, 2017**	17	ToM reading
McAdams*, 2013	18	Frith-Happé	**Littlefield*, 2015**	23	ToM reading/faces	**Massau*, 2017**	50	Moral judgement of others' behavior
Saft*, 2013	26	ToM cartoon	**Mohnke*, 2015**	297	ToM cartoon	**Mier*, 2017**	44	ToM reading/faces
Schiffer*, 2013	22	Reading the Mind in the Eyes	**Otti*, 2015**	20	Frith-Happé	**Özdem*, 2017**	21	Eye gaze evaluation
van der Meer*, 2013	19	False belief	**Schlaffke*, 2015**	39	ToM cartoon	**Powell* 2017**	12	Predict peer strategy during game
Varga*, 2013	24	Irony	**Schurz*, 2015**	22	Visual perspective taking	**White*, 2017**	23	Pain/harm in others
Ampe*, 2014	17	Action identification (images)	**Spunt*, 2015**	480	False belief	**White*, 2017**	23	Pain/harm in others
Dodell-Feder*, 2014	18	ToM reading	**Wang*, 2015**	56	ToM cartoon	**Ammons*, 2018**	14	Frith-Happé
Dodell-Feder*, 2014	18	False belief	**Willert*, 2015**	81	ToM cartoon	**Bartholomeusz*, 2018**	22	ToM cartoon
Feng*, 2014	17	Humor	**Bardi*, 2016**	22	False belief	**Bitsch*, 2018**	20	Prisoner's dilemma
Hartwright*, 2014	20	False belief	**Dungan*, 2016**	24	False belief	**Bliksted*, 2018**	17	Frith-Happé
Lee*, 2014	19	False belief	**Eddy* 2016**	50	False belief	**Grant*, 2018**	50	ToM reading
Mier*, 2014	18	ToM reading/faces	**Hennion*, 2016**	25	Frith-Happé	**Herold*, 2018**	12	Irony
Reniers*, 2014	15	ToM faces	**Jacoby*, 2016**	20	False belief	**Lee*, 2018**	16	Pain/harm in others
Riekki*, 2014	23	Frith-Happé	**Kirkovski*, 2016**	23	Frith-Happé	**Lin*, 2018**	39	ToM reading
Schneider*, 2014	16	False belief	**Lavoie*, 2016**	19	ToM reading	**Niemi*, 2018**	16	Moral judgements of others
Schuwerk*, 2014	21	False belief	**Schmitgen*, 2016**	21	ToM cartoon	**Nijhof*, 2018**	21	False belief
First author, year	**N**	**Task type**	**First author, year**	**N**	**Task type**	**First author, year**	**N**	**Task type**
Ohtsubo*, 2018	37	Others apologizing	**Tsoi*, 2018**	25	Pain/harm in others	**Lassalle*, 2019**	20	Pain/harm in others
Sommer*, 2018	15	False belief	**Wurm*, 2018**	18	Action identification (images)	**Zhu*, 2019**	30	Guilt/shame in others

Specht*, 2018	18	ToM cartoon	**Zhang*, 2018**	58	Ambiguous ToM reading			
Thye*, 2018	18	Reading the Mind in the Eyes	**Greven*, 2019**	25	Body judgement of others			

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

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

First author, year	**N**	**Age [mean age±SD/range in years]**	**Task type**	**Contrast**	***p* value, correction†**
Ohnishi*[1], 2004	11	[10.0/7–13]	**Frith–Happé**	ToM animation>Control	$p<0.05$ uc
Wang*[1], 2006	12	[11.9±1.8/9–14]	**Irony**	Irony>Control	SVC at $p<0.05$, $k\geq37$
Blakemore*[2], 2007	19	[14.8/12–18]	**ToM reading**	ToM statements>Physical causality	Random fields theory corr. or SVC at $p<0.05$
Kobayashi*[1], 2007	24	[9.1±1.2/8–11]	**False belief**	False belief>Physical causality	$p<0.005$ uc
Moriguchi*[2], 2007	16	[13.4±2.2/9–16]	**Frith–Happé**	ToM animation>Control condition	$p<0.001$ uc, $k\geq50$
Pfeifer*[1], 2007	12	[10.2/9–10]	**Self-referential thinking (auditory)**	Self>Social knowledge	$p<0.005$ uc, $k\geq10$
Burnett*[2], 2008	19	[14.8/11–18]	**Guilt/embarrassment in others or self**	Social (guilt/ embarrassment)>Basic emotion (disgust/fear)	SVC at $p<0.05$
Decety*[1], 2008	17	[9.0/7–12]	**Pain in others**	Pain>No pain (body parts)	$p<0.005$ uc, $k\geq8$
Kobayashi*[1], 2008	12	[10.1±1.0/8–11]	**False belief**	False belief>Physical causality	$p<0.005$ uc

Pfeifer*[2], 2009	12	[12.7/11–13]	**Self-referential thinking (auditory)**	Self>Social knowledge	Corr. at p<0.05
Saxe*[1], 2009	13	[8.7/6–10]	**Auditory ToM**	Mental state stories>Physical facts	*p*<0.001 uc, k≥5
Sommer*[1], 2010	10	[11.3±0.7/10–12]	**False belief**	False>True belief	Cluster-level corr. or SVC at p<0.01
Gweon*[1], 2012	20	[8.5/5–11]	**ToM reading**	ToM statements>Physical causality	Monte-Carlo simulation corr. at p<0.05, k≥200
Schulte-Rüther*[2], 2012	21	[15.8±1.9/12–18]	**Frith–Happé**	ToM animation>Control	Voxel-level FWE corr., k≥30
Sebastian*[2], 2012	47	[14.1±1.7/10–16]	**False belief**	Affective ToM>Physical causality, Cognitive ToM>Physical causality	Cluster-level FWE corr. at p<0.05
Yokota*[1], 2013	28	[8.9/8–9]	**ToM cartoon**	Social>Less social	Cluster-level FWE corr. at p<0.05
O'Nions*[2], 2014	48	[13.9±1.7/10–16]	**False belief**	Cognitive ToM>Control	Peak-level FWE corr. at p<0.05
Overgaauw*[2], 2014	32	[15.5/12–19]	**Reading the Mind in the Eyes**	Mental state>Control	FDR corr. at p<0.05, k≥10
White*[2], 2014	33	[13.7/11–17]	**False belief**	Cognitive ToM>Control	FWE corr. at p<0.05
Kana*[2], 2015	13	[12.7/10–15]	**Frith–Happé**	ToM animation>Control	Monte-Carlo simulation corr. at p<0.05, k≥100
Alkire*[1], 2018	28	[10.4±1.5/8–12]	**Predict peer strategy during game**	Mental state prediction>Control	Cluster-level corr. at p<0.05, k≥86
Mukerji*[1], 2019	32	[11.1±1.4/9–12]	**False belief**	False belief>False photograph	p<0.001 uc, k≥10 or FWE corr. at p<0.05

*=only first authors are listed, N=number of participants, SD=standard deviation, ToM=Theory of Mind,

†=correction is not accounted for in the resulting meta-analysis, Frith-Happé=Frith-Happé animations or adaptations, ToM cartoon=comics or cartoons eliciting mentalizing, ToM reading=sentences or statements eliciting mentalizing, uc=uncorrected, corr.=corrected, SVC=small volume correction, FWE=family-wise error rate, k=number of voxels in cluster. [1]studies entering the subgroup analyses in children, [2]studies entering the subgroup analyses in adolescents. The full references of this table can be found in Supplementary Information 6.

2.2. Meta-analytic methods

2.2.1. Activation likelihood estimation meta-analyses

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

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

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

2.2.2. Meta-analytic connectivity modeling

Meta-analytic connectivity modeling (MACM) was used to explore functional connectivity during mentalizing in adults. MACM derives patterns of neural coactivation with studies in the BrainMap database (Fox & Lancaster, 2002; Robinson et al., 2012; Robinson et al., 2010). Analyses were conducted for adults only since the studies included in the BrainMap database (www.brainmap.org) used for connectivity modeling are almost exclusively based on adult literature. Consequently, no meta-analytic connectivity modelling using children/adolescents was possible. Individual steps for connectivity modelling are described in **Supplementary Information 4**. In short, three analyses were conducted: 1) Connectivity analyses for which all duplicates between the meta-analysis in adults and the BrainMap search findings were omitted (i.e., studies investigating mentalizing in adults that were already included in our own meta-analyses), 2) all paradigms of the BrainMap database entered the analysis (including Theory of Mind/mentalizing tasks), 3) connectivity analyses for each of the 9 ROIs individually based on all paradigms in the BrainMap database were repeated to report which specific region was co-activated with any other area in the brain.

3. Results

3.1. Activation likelihood estimation meta-analysis results

The individual ALE meta-analysis for 206 functional neuroimaging studies of mentalizing in adults revealed 9 significant clusters of activation, including bilateral temporoparietal junction extending into the middle temporal gyrus, precuneus and medial and inferior/middle frontal gyri. The individual ALE meta-analysis on 22 studies in children/adolescents resulted in 7 significant clusters of activation, including ventromedial and middle medial frontal cortex, bilateral temporoparietal junction, precuneus/posterior cingulate gyrus and middle/superior temporal gyri. The conjunction analysis examining the overlap of activation in studies in adults and children/adolescents resulted in 7 clusters of brain activation reflecting mentalizing and included ventromedial and middle medial prefrontal cortex, precuneus, bilateral temporoparietal junction and middle/superior temporal gyri (**Figure 1A, Table 3**). Finally, the contrast analysis for increased activation during mentalizing for adults compared to children/adolescents, based on a robust test including resampling of the adult studies, resulted in a total of 42 clusters (18 clusters with a volume of >100 voxels), in areas including superior medial frontal cortex, bilateral superior/middle/inferior frontal gyri, posterior temporoparietal junction (including middle temporal gyri and superior parietal lobule), posterior precuneus, thalamus, claustrum/insula and right occipital pole (**Figure 1B, Table 4,** full list of clusters in **Supplementary Information 7**, entire output at https://osf.io/fe5vu/). The contrast analysis for increased activation for children/adolescents compared to adults yielded 8 clusters (7 clusters with a volume of >100 voxels), including ventromedial and middle medial prefrontal cortex, precuneus, bilateral temporoparietal junction and middle/superior temporal gyri (**Figure 1B, Table 4,** https://osf.io/fe5vu/). The added conjunction analysis based on the resampling approach yielded 7 clusters which were highly similar (i.e., including the same regions) to the initial conjunction analysis (**Figure 1B, Table 4**, https://osf.io/fe5vu/).

To investigate potential confounds introduced by task variability, we conducted additional analyses using more restrictive criteria of including Theory of Mind tasks only (e.g., false belief tasks, Frith–Happé animations, Theory of Mind cartoon tasks). This led to comparable results (**Supplementary Information 5**). Notably, the right middle frontal gyrus previously detected in adults and the ventromedial prefrontal cortex reported in children and the conjunction were no longer significant. However, when using more lenient statistics (a cluster forming threshold of $p<0.001$, uncorrected), activation in both the right middle frontal gyrus (adults) and ventromedial prefrontal cortex (children, conjunction) were also visible.

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

Cluster	Region	H	Vol	Weighted center			Local maxima			BA	ALE extrema
Adults				x	y	z	x	y	z		
1	Superior/middle temporal gyrus	L	27048	-54	-39	6	-52	-58	24	39	0.16314
							-56	-10	-16	21	0.09503
							-56	-48	4	22	0.08342
							-58	-44	4	22	0.08245
							-54	-2	-24	21	0.08228
							-54	2	-28	21	0.08187
							-52	-34	-4	21	0.07534
							-62	-20	-10	21	0.06008
							-48	10	-36	38	0.05558
2	Superior/middle temporal gyrus	R	22896	54	-32	2	56	-54	26	39	0.14155
							56	-54	18	39	0.13739
							54	-2	-22	21	0.11530
							60	-8	-18	21	0.10536
							50	8	-30	21	0.07466
							46	14	-32	38	0.06757
							52	-34	-2	-	0.06248
							50	-72	8	37	0.05878
3	Middle medial/superior frontal gyrus	L/R	20704	-1	54	20	-6	56	32	8	0.12811
							0	46	-18	10	0.07336
							2	54	-12	10	0.06272
							2	44	44	8	0.04970
							4	38	38	8	0.04734
							4	42	34	6	0.04575

4	Inferior frontal gyrus	L	11120	-48	24	3	-54	24	8	45	0.09785
							-48	28	-10	47	0.09691
							-42	10	28	9	0.05533
5	Precuneus	L	10680	1	-55	35	-2	-54	36	31	0.15210
6	Inferior/middle frontal gyrus	R	8112	50	26	7	56	28	8	45	0.10600
							52	30	-6	45	0.07474
							48	22	22	46	0.06643
							36	24	-12	47	0.05135
7	Medial superior frontal gyrus	L/R	4992	-5	19	56	-4	18	56	6	0.07184
							-4	18	52	6	0.07093
							8	24	54	8	0.03584
8	Middle frontal gyrus	L	2344	-43	5	51	-44	6	52	6	0.06286
9	Middle frontal gyrus	R	1896	44	9	45	44	8	44	6	0.05884
Children/adolescents											
1	Medial/superior frontal gyrus	R	3224	2	56	21	4	56	20	9	0.03730
							10	56	32	8	0.01775
2	Superior/middle temporal gyrus	L	2864	-45	-58	23	-46	-58	22	39	0.02365
							-42	-58	20	22	0.02262
3	Precuneus, posterior cingulate gyrus	L	2536	-1	-54	33	0	-54	34	31	0.02384
							0	-50	24	30	0.01660
4	Middle/superior temporal gyrus	R	2008	52	8	-26	54	2	-24	21	0.02020
							52	12	-24	38	0.01934
							46	14	-32	38	0.01530
5	Superior temporal gyrus, supramarginal gyrus, inferior parietal lobule	R	1384	52	-58	21	50	-58	20	22	0.02618
							58	-52	24	40	0.01311
							54	-46	24	40	0.01189
6	Medial frontal gyrus	R	1368	2	55	-9	0	54	-8	-	0.02087
							2	50	-18	10	0.01329
7	Middle/inferior temporal	L	1200	-56	-4	-21	-56	-2	-22	21	0.02409

	gyrus						-58	-14	-22	21	0.01316
Conjunction: Adults ∩ children/adolescents											
1	Medial/superior frontal	R	2912	2	56	21	4	56	20	9	0.03730
	gyrus						10	56	32	8	0.01775
2	Superior/middle temporal	L	2624	-46	-58	23	-46	-58	22	39	0.02365
	gyrus						-42	-58	20	22	0.02262
3	Precuneus, posterior	L	2448	-1	-54	34	0	-54	34	31	0.02384
	cingulate gyrus						0	-50	24	30	0.01660
4	Middle/superior temporal	R	1736	52	7	-26	54	2	-24	21	0.02020
	gyrus						52	12	-24	38	0.01934
							46	14	-32	38	0.01530
5	Superior temporal gyrus,	R	1320	52	-57	21	50	-58	20	22	0.02618
	supramarginal gyrus,						58	-52	24	40	0.01311
	inferior parietal lobule						54	-46	24	40	0.01189
6	Middle/inferior temporal	L	1128	-56	-4	-21	-56	-2	-22	21	0.02409
	gyrus						-58	-14	-22	21	0.01316
7	Medial frontal gyrus	R	888	1	54	-10	0	54	-8	-	0.02087
							2	50	-18	10	0.01329

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

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

Cluster	**Region**	**H**	**Vol**	**Coordinates**		
Adults > children/adolescents				x	y	z
1	Medial frontal gyrus, pre-supplementary	L	2132	-2	58	32

	motor area					
2	Temporoparietal junction, inferior parietal lobule, angular gyrus, supramarginal gyrus	L	1925	-58	-54	22
3	Inferior parietal lobule, angular gyrus, middle temporal gyrus	R	1162	56	-52	16
4	Inferior frontal gyrus	R	919	58	32	4
5	Inferior frontal gyrus, frontal orbital cortex	L	825	-48	26	-12
6	Middle frontal gyrus	L	658	-42	8	52
7	Anterior middle temporal gyrus	R	528	58	-8	-18
8	Middle frontal gyrus	L	366	-43	5	51
9	Precuneus	R	309	4	-62	30
10	Middle frontal gyrus	R	163	40	8	38
11	Superior parietal lobule, intraparietal sulcus	L	161	-34	-54	40
12	Insula	L	156	-30	24	-6
13	Inferior lateral occipital cortex	R	155	32	-96	-10
14	Cerebellum (crus)	L	152	-28	-76	-34
15	Superior/middle frontal gyurs	L	134	-20	30	34
16	Thalamus	R	129	8	-24	-6
17	Anterior middle temporal gyrus	R	117	50	6	-38
18	Thalamus	L	116	-10	-18	2
Children/adolescents > adults						
1	Medial superior frontal gyrus	R	353	2	56	20
2	Inferior parietal lobule, angular gyrus	L	318	-42	-60	28
3	Precuneus, posterior cingulate gyrus	L/R	307	0	-50	28
4	Temporal pole, middle temporal gyrus	R	242	54	10	-22
5	Medial frontal gyrus, frontal pole	R	168	6	58	-4
6	Inferior parietal lobule, angular gyrus	R	130	48	-60	20

7	Middle/superior temporal gyrus	L	129	-56	-2	-20
Conjunction: Adults ∩ children/adolescents						
1	Medial/superior frontal gyrus	R/L	372	0	56	26
2	Inferior parietal lobule, angular gyrus	L	312	-50	-58	24
3	Precuneus, posterior cingulate gyrus	L	305	-2	-54	36
4	Middle/superior temporal gyrus	R	222	52	0	-24
5	Middle temporal gyrus	L	125	-56	-4	-20
6	Inferior parietal lobule, angular gyrus	R	120	54	-56	18
7	Medial frontal cortex	R/L	113	0	52	-12

H=Hemisphere, R=right; L=left, Vol=Volume in voxels, x, y, z coordinates are in Montreal Neurological Institute (MNI) space.

3.2. Follow-up analyses: Mentalizing in younger children and adolescents

The ALE meta-analysis for children (average age below 12 years) resulted in 4 significant clusters of activation including bilateral medial frontal gyri, precuneus and right temporoparietal junction. In adolescents (average age above 12 years) 5 significant clusters of activation were identified in middle medial prefrontal cortex, bilateral temporoparietal junction/superior temporal gyri, middle and inferior temporal gyri and cingulate gyrus extending into precuneus. The conjunction analysis of both age groups resulted in 2 clusters of significant common activation across both groups including middle medial prefrontal cortex and precuneus/posterior cingulate cortex (**Figure 1C/ Table 5**).

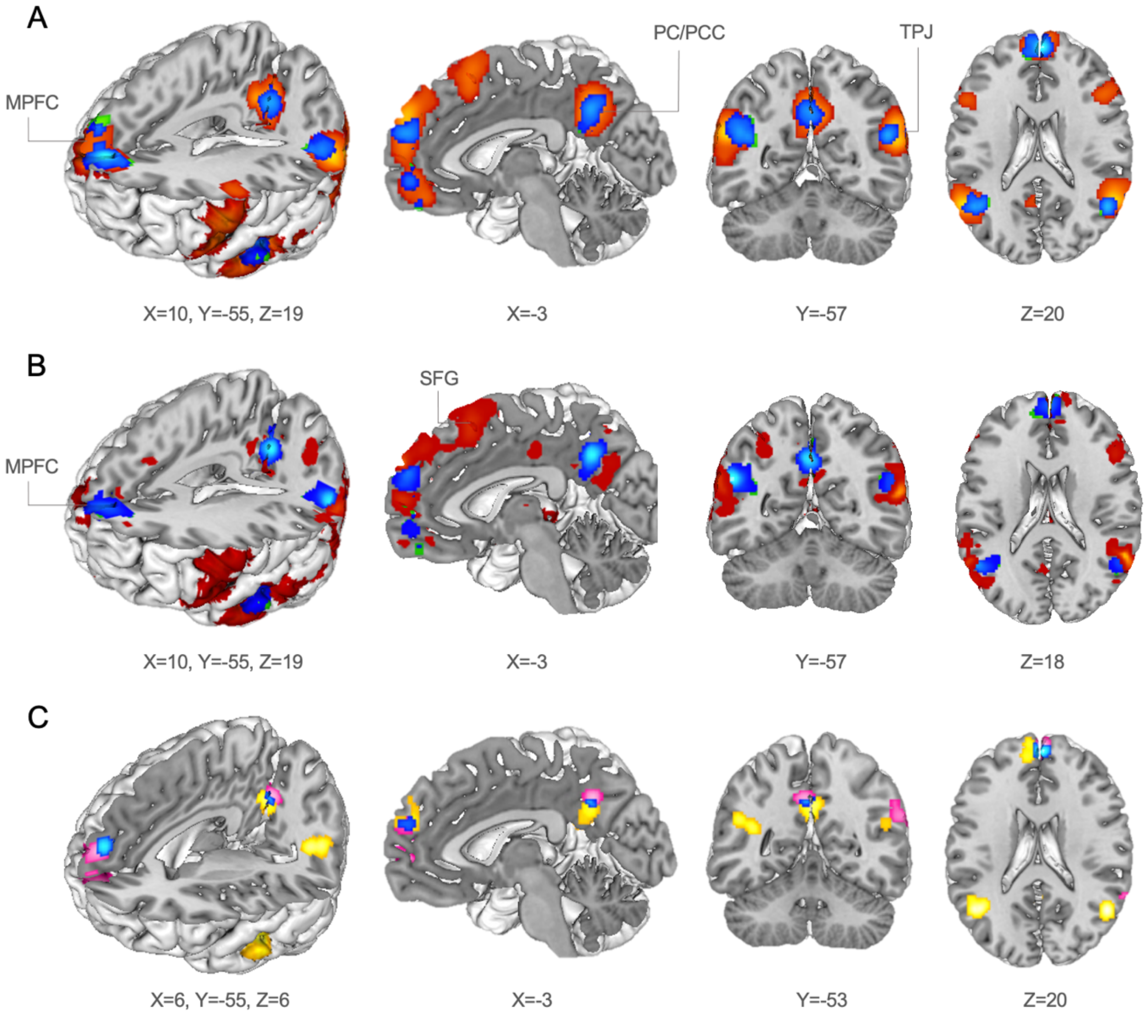

Figure 1. Overlay of meta-analysis results for **(A)** adults (red) and children/adolescents (green; almost fully covered since overlapping with the conjunction results) and the conjunction analysis of both groups (blue) during mentalizing. Overlapping brain activity in adults and children/adolescents was identified for medial prefrontal cortex (MPFC), precuneus (PC)/posterior cingulate gyrus (PCC), temporoparietal junction (TPJ) and middle temporal gyri. **(B)** contrast analyses for adults > children/adolescents (red) and children/adolescents > adults (green; almost fully covered since overlapping with the conjunction results) and the conjunction analysis of both groups (blue) during mentalizing. Increased activity for adults compared to children was for example detected in middle medial prefrontal cortex (MPFC), superior and inferior frontal gyri (SFG/IFG) and middle temporal gyri (MTG). **(C)** Children (below 12 years of age; pink), adolescents (12 years and older; yellow), and the conjunction analysis of both age groups (blue). Common brain activity was detected in MPFC and PC/PCC (all $p<0.05$, FWE corrected).

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

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

H=hemisphere, R=right, L=left, Vol=volume in mm^3, BA=Brodmann Area. x, y, z coordinates are in Montreal Neurological Institute (MNI) space.

3.3. Meta-analytic connectivity modeling

By December 2019, the BrainMap database contained 3406 publications with 16901 contrasts and 76016 subjects. The BrainMap search results for each ROI are listed in **Table 6**. Results include paradigms for e.g., motor tasks/button press, semantic discrimination or face discrimination. The MACM analysis for all ROIs together (identical to the meta-analytic results in adults) revealed functional connectivity with bilateral middle and inferior frontal gyri extending into insula, medial superior frontal gyri, bilateral superior temporal gyri, left inferior parietal lobule extending into supramarginal gyrus, right superior parietal lobule and bilateral thalamus/basal ganglia (caudate, putamen, globus pallidus; results in **Figure 2** and **Table 7)**. The connectivity results including all paradigms in the BrainMap database and for each ROI separately are reported in **Supplementary Information 8 and 9**, respectively**.**

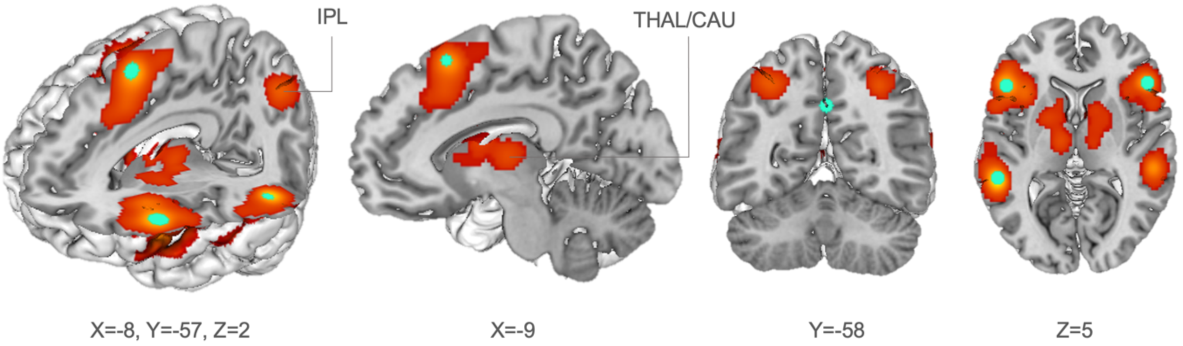

Figure 2. Meta-analytic connectivity modeling results for adults. Regions of interest identified in our meta-analysis (mint) and resulting clusters of functional connectivity (red), including inferior parietal lobule (IPL) and thalamus/caudate (THAL/CAU). Coordinates are in MNI space.

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

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

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

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

Cluster	Region	H	Vol	Weighted center			Local maxima			BA	ALE extrema
				x	y	z	x	y	z		
1	Middle/inferior frontal gyrus	L	39648	-45	16	20	-44	4	50	6	0.26320
							-48	26	2	45	0.21631
							-46	18	22	9	0.15168
2	Inferior/middle frontal gyrus, insula	R	28752	46	18	16	50	26	8	45	0.19116
							44	10	46	6	0.15275

							38	22	-6	–	0.13327
							46	18	-4	13	0.10349
							52	22	28	9	0.08854
							48	12	26	9	0.08448
							48	34	24	9	0.05953
							46	38	24	9	0.05867
3	Medial superior frontal gyrus	L	20424	0	18	48	-4	18	54	6	0.26774
4	Middle/superior temporal gyrus	L	10968	-56	-37	5	-54	-40	6	22	0.26631
							-58	-6	-6	22	0.07007
5	Inferior parietal lobule, supramarginal gyrus	L	9656	-35	-52	46	-32	-52	48	40	0.11232
							-46	-38	42	40	0.07748
6	Superior temporal gyrus	R	7032	56	-32	2	54	-32	2	22	0.18224
							62	-16	0	22	0.05018
							62	-40	14	22	0.04970
							56	-46	10	22	0.04956
							58	-6	-2	22	0.04817
7	Thalamus, caudate, globus pallidus	L	5568	-13	-4	7	-10	-14	6	–	0.08201
							-12	2	14	–	0.07733
							-18	2	6	–	0.06834
8	Globus pallidus, caudate, putamen, thalamus	R	4736	16	-1	7	14	2	0	–	0.06502
							14	8	8	–	0.06335
							20	2	8	–	0.06294
							12	-14	8	–	0.06068
9	Superior parietal lobule	R	4504	34	-55	49	34	-54	48	7	0.09201
							28	-64	56	7	0.07454

H=Hemisphere, R=right; L=left, Vol=Volume in mm^3, x, y, z coordinates are in Montreal Neurological Institute (MNI) space, BA=Brodmann Area (if applicable)

[1] Co-activation with 5mm spheres around bilateral superior/middle temporal gyri (-54 -39 6, 54 -32 2), medial middle (-1 54 20), medial superior (-5 19 56), middle (-43 5 51, 44 9 45), and inferior frontal gyri (-48 24 3, 50 26 7) and precuneus (1 -55 35)

4. Discussion

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

Across children, adolescents and adults, consistent recruitment of medial prefrontal cortex, precuneus and temporoparietal junction was observed. Medial prefrontal cortex and temporoparietal junction are commonly associated with mentalizing (Mar, 2011; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle, 2009; van Veluw & Chance, 2014). The medial prefrontal cortex has been suggested to play a generic role when reasoning about one's own or others' mental states (Amodio & Frith, 2006; Blakemore, 2008; Molenberghs et al., 2016; Moll & de Oliveira-Souza, 2007; Shamay-Tsoory et al., 2009). The ventromedial prefrontal cortex is more strongly related to social emotion processing or regulation of emotions (Hiser & Koenigs, 2018). The temporoparietal junction is prominently recruited using false belief or perspective taking tasks (Decety & Lamm, 2007), and has been suggested to comprise of a subregion selective for reasoning about others' mental states (Saxe & Kanwisher, 2003; Van

Overwalle, 2009). Tasks involving the reorientation of attention and representing a sense of agency have likewise shown to lead to activation increases in temporoparietal regions (Decety & Lamm, 2007). Finally, the precuneus has been suggested to play a significant role in memory and mental imagery needed to construct different perspectives (Cavanna & Trimble, 2006; Schurz et al., 2013). Overall, brain regions showing activation during mentalizing across development have been broadly linked to the reorientation of attention, memory processes and mental imagery. Such patterns of neural engagement may indicate that the neural basis supporting mentalizing is somewhat stable from a young age on, possibly reflecting an early specialization of parts of the social brain (Bowman et al., 2019). Our findings are supported by behavioral evidence of mentalizing skills starting to develop early in life and continuing until young adulthood (Blakemore, 2008; Knudsen & Liszkowski, 2012; Meins et al., 2002).

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

Our follow-up subgroup analyses investigating younger children (<12 years) and adolescents (>12 years) revealed that children up to 12 years of age commonly engage brain areas within the middle medial prefrontal cortex, precuneus and right temporoparietal junction, while adolescents commonly activate a more adult-like set of brain regions, including medial prefrontal cortex, precuneus, bilateral temporoparietal junction and anterior middle/inferior temporal cortices (Mar, 2011; Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle, 2009; van Veluw & Chance, 2014). In the present meta-analyses, development of the temporoparietal junction is indicated by unilateral (i.e., right-hemispheric) activation in children, but bilateral activation in adolescents. Notably, interpretation is limited by the small number of studies and by the cross-sectional designs included. Thus, the present results may broadly point towards developmental effects based on categorical observations only (Blakemore, 2008, 2012b). Brain maturation, especially of prefrontal brain regions, is paralleled by increasing mentalizing skills and cognitive development across age (Blakemore et al., 2007a; Blakemore, 2008, 2012a, 2012b; Crone & Dahl, 2012), while development of temporoparietal junction is suggested to underlie an increasing selectivity for mental state processing (Gweon et al., 2012; Saxe et al., 2009). In adults, functional connectivity between areas of the social brain network (i.e., bilateral superior/middle temporal gyri, precuneus, medial superior frontal gyri and bilateral middle and inferior frontal gyri) and further connectivity to bilateral thalamus, basal ganglia and inferior and superior parietal lobule was observed. The rostral section of the inferior parietal lobule (Brodmann Area 40; (Brodmann, 1909)) and the superior parietal lobule are located dorsally of the temporoparietal junction. The inferior parietal lobule forms part of the mirror neuron system and is involved in the imitation of actions needed to adapt to social situations and when processing semantic and affective information (Caspers et al., 2010; Iacoboni, 2009; Molenberghs et al., 2009), whereas the superior parietal lobule is implicated in working memory and visuospatial attention (Corbetta et al., 1995; Koenigs et al., 2009). The thalamus and basal ganglia (e.g., striatum, composed by the caudate nucleus and putamen) are implicated in reward-based learning and higher-level behavioral control and regulation (e.g., (DeLong & Wichmann, 2009)). Connectivity between the thalamus/basal ganglia and the cerebral cortex (e.g., dorsolateral prefrontal cortex, anterior cingulate cortex) has been commonly reported in emotion processing and higher-order cognitive processes such as mentalizing (Di Martino et al., 2008; Molenberghs et al., 2016; Postuma & Dagher, 2006). Inclusion of Theory of Mind tasks in the paradigms entering the connectivity analyses led to an additional coactivation cluster in the middle medial prefrontal cortex, which may indicate that this area is specifically activated during mentalizing (Molenberghs et al., 2016; Schurz et al., 2014). For developmental populations, only few studies so far have examined functional connectivity during mentalizing. Burnett and Blakemore (2009) reported increased functional connectivity between the ventromedial prefrontal cortex and left temporoparietal junction/posterior superior temporal sulcus in adolescents compared to adults, possibly reflecting increasing specialization of the network connections during skill development. Similarly, Richardson and colleagues (2018) detected increased connectivity with age between temporoparietal junction, precuneus and medial prefrontal cortex in children aged 3–12 years during an implicit Theory of Mind task. Others reported no age effects in connectivity during mentalizing, but stable connectivity patterns between associated areas (e.g., medial prefrontal cortex, temporoparietal junction, precuneus) and striatum/dorsolateral prefrontal cortex ((McCormick et al., 2018); in 8–16-year-olds) or within mentalizing regions (temporoparietal junction, superior temporal sulcus, precuneus (Mukerji et al., 2019); in 9–13-year-olds). Such differences in findings may arise due to variations in the tasks employed or the characteristics of the group studied.

4.1.Limitations and future steps

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

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

4.2. Conclusion

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

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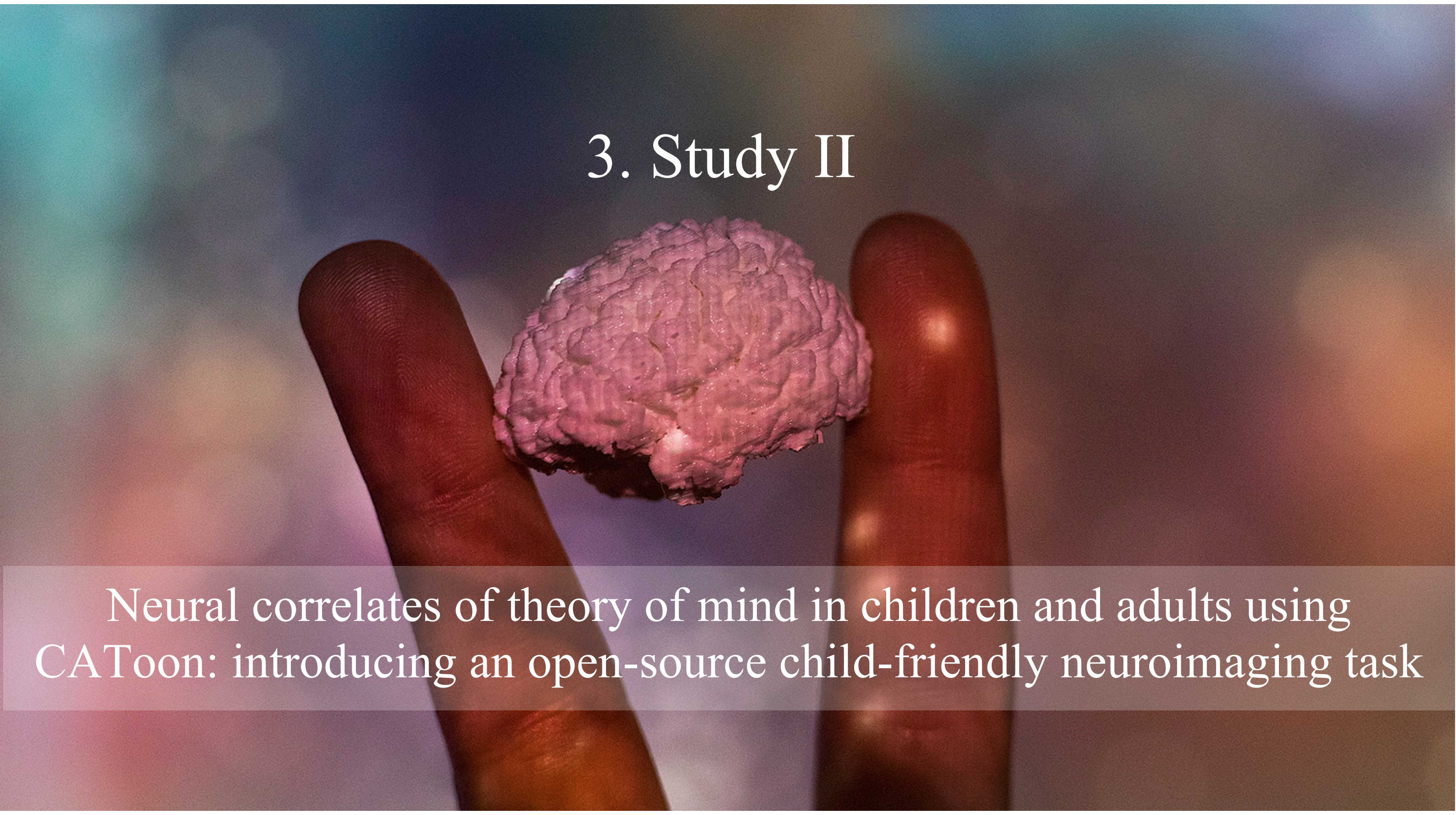
Supplementary material is available at Social Cognitive and Affective Neuroscience online.



3. Study II

Neural correlates of theory of mind in children and adults using CAToon: introducing an open-source child-friendly neuroimaging task

Réka Borbás[1,2], *Lynn V. Fehlbaum*[1,2], *Ursula Rudin*[2], *Christina Stadler*[2], *Nora M. Raschle*[1,2]

[1] *Jacobs Center for Productive Youth Development at the University of Zurich, Zurich, Switzerland*

[2] *Department of Child and Adolescent Psychiatry, University of Basel, University Psychiatric Clinics Basel, Basel, Switzerland*

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Abstract

Theory of mind (ToM) or mentalizing is a basic social skill which is characterized by our ability of perspective-taking and the understanding of cognitive and emotional states of others. ToM development is essential to successfully navigate in various social contexts. The neural basis of mentalizing is well-studied in adults, however, less evidence exists in children. Potential reasons are methodological challenges, including a lack of age-appropriate fMRI paradigms. We introduce a novel child-friendly and open-source ToM fMRI task, for which accuracy and performance were evaluated behaviorally in 60 children ages three to nine (32♂). Furthermore, 27 healthy young adults (14♂; mean =25.41 years) and 33 children ages seven to thirteen (17♂; mean = 9.06 years) completed the **C**ognitive and **A**ffective **T**heory of Mind Cart**oon** task (**CAToon;** www.jacobscenter.uzh.ch/en/research/developmental_neuroscience/downloads/catoon.html) during a fMRI session. Behavioral results indicate that children of all ages can solve the CAToon task above chance level, though reliable performance is reached around five years. Neurally, activation increases were observed for adults and children in brain regions previously associated with mentalizing, including bilateral temporoparietal junction, temporal gyri, precuneus and medial prefrontal/orbitofrontal cortices. We conclude that CAToon is suitable for developmental neuroimaging studies within an fMRI environment starting around preschool and up.

1. Introduction

Theory of Mind (ToM), or mentalizing, describes our ability to represent and understand the mental states (feelings, beliefs, desires and intentions) of others and ourselves (Gallagher & Frith, 2003). ToM is an essential social skill (Frith & Frith, 2008; Korkmaz, 2011; Saxe, 2006; Schnell, Bluschke, Konradt, & Walter, 2011) and a failure to develop adequate ToM skills is associated with different neurodevelopmental disorders, including autism spectrum disorder, developmental language disorder, attention deficit hyperactivity disorder and conduct disorder (Clegg, Hollis, Mawhood, & Rutter, 2005; Frith, 2001; Sebastian, McCrory, et al., 2012; Senju, 2012; Sharp, 2008; Uekermann et al., 2010). ToM may be differentiated into an affective (the understanding of emotions of others) and cognitive subcomponent (inferences a person makes about other people's beliefs and intentions; (Shamay-Tsoory, Harari, Aharon-Peretz, & Levkovitz, 2010)). Behaviorally, ToM has commonly been associated with empathy (O'Connell, 1995; Saxe, 2006; Völlm et al., 2006; Walter, 2012), and functional neuroimaging evidence indicates a partial overlap of brain regions commonly associated with empathy and mentalizing (Bzdok et al., 2012; Powell, Grossi, Corcoran, Gobet, & Garcia-Finana, 2017; Völlm et al., 2006).

The foundations of mentalizing are laid during the first few years of life, though they become more refined throughout childhood and adolescence. Early conceptualizations of ToM tasks have particularly focused on explicit measures (e.g., Sally and Anne Task (Baron-Cohen, Leslie, & Frith, 1985)), which are mastered around the age of 4 (Baron-Cohen et al., 1985; Wimmer & Perner, 1983). However, studies employing implicit ToM assessments during infancy, as for example through the investigation of an infant's anticipatory looks, have suggested that ToM may develop as early as 13-15 months (Onishi & Baillargeon, 2005; Southgate, Senju, & Csibra, 2007; Surian, Caldi, & Sperber, 2007). Consequently, the type of task employed to measure ToM, or mentalizing, may have a significant influence on the interpretation of the reported skill levels.

Studies assessing the neural correlates of ToM in adults (Bzdok et al., 2012; Molenberghs, Johnson, Henry, & Mattingley, 2016; Van Overwalle & Baetens, 2009) have consistently linked mentalizing to brain areas within the frontal (e.g., anterior dorsal medial and ventromedial PFC, inferior frontal- and precentral gyri and the anterior cingulate cortex), temporal and parietal cortices (e.g., bilateral temporoparietal junction, middle temporal gyri, posterior superior temporal sulci and the precuneus (Molenberghs et al., 2016)). In accordance with the conceptual separation of affective and cognitive ToM, distinct networks can be identified (2013; Schlaffke et al., 2015; Sebastian et al., 2012; Shamay-Tsoory & Aharon-

Peretz, 2007). While affective and cognitive mentalizing are controlled by a shared network comprising bilateral temporal poles, superior temporal sulci and the dorsomedial prefrontal cortex, the specific role of orbitofrontal and ventromedial prefrontal cortices in affective mentalizing has been highlighted based on research in clinical and healthy populations (Hynes, Baird, & Grafton, 2006; Sebastian et al., 2012; Shamay-Tsoory & Aharon-Peretz, 2007). Affective ToM has also particularly been associated with basal ganglia functioning (Schlaffke et al., 2015; Bodden et al., 2013). On the other hand, cognitive mentalizing processes are more specifically linked to activation in the dorsomedial prefrontal cortex, precuneus, cuneus, bilateral temporoparietal junction, and the middle of the superior temporal gyri (Molenberghs et al., 2016; Van Overwalle & Baetens, 2009; Schlaffke et al., 2015).

While various reports describe the neural correlates of ToM in adults, less is known for younger children, with or without neurodevelopmental disorders. Potential reasons may include practical and technical challenges as well as a lack of age-adequate scanner tasks (Raschle et al., 2012; Raschle et al., 2009; Thieba et al., 2018). However, in recent years new studies have emerged investigating mentalizing in young populations through task-based functional magnetic resonance imaging (fMRI) or functional near infrared spectroscopy (Gweon, Dodell-Feder, Bedny, & Saxe, 2012; Hyde, Simon, Ting, & Nikolaeva, 2018; Moraczewski, Chen, & Redcay, 2018; Richardson, Lisandrelli, Riobueno-Naylor, & Saxe, 2018; Richardson & Saxe, 2020a). Such studies implement auditory paradigms, false belief tasks or incorporate more naturalistic settings such as passive movie viewing tasks. Alternatively, task-free functional (e.g., resting state fMRI (Xiao, Geng, Riggins, Chen, & Redcay, 2019)) or structural measures, (e.g., white matter measures (Wiesmann, Schreiber, Singer, Steinbeis, & Friederici, 2017)) can be further substantiated through the use of additional behavioral ToM measures.

Here we present three experimental studies conducted to assess the development and implementation of the ***C**ognitive and **A**ffective **T**heory of Mind Cart**oon** task* (in short **CAToon;** available at: www.jacobscenter.uzh.ch/en/research/developmental_neuroscience/downloads/catoon.html), a novel, open-source, engaging and child-friendly fMRI mentalizing task. **Study 1** introduces development and behavioral assessment of CAToon in children. Specifically, we aimed to assess the age at which children were able to complete CAToon behaviorally. We hypothesized that CAToon may be completed starting around preschool/kindergarten (around 4 years of age).

Study 2 aimed to investigate whether CAToon will reliably elicit activation in brain regions previously associated with mentalizing in adults. Activation increases were expected in brain regions including dorsomedial PFC, bilateral temporoparietal junction, middle medial PFC, precuneus, right superior temporal sulcus, and ventromedial PFC (Molenberghs et al., 2016). Furthermore, affective and cognitive stories were hypothesized to elicit distinct (cognitive ToM: dorsomedial PFC, precuneus, superior temporal gyrus; affective ToM: OFC, ventromedial PFC, bilateral pars opercularis, basal ganglia,) as well as shared neural activation patterns (e.g., dorsomedial PFC, bilateral temporoparietal junction; (Bodden et al., 2013; Dufour et al., 2013; Hynes et al., 2006; Völlm et al., 2006)).

Study 3 aimed to assess the neural correlates during CAToon performance in a first group of typically developing children. We hypothesized, that CAToon may elicit similar, though still developing neuronal activation patterns in children (Richardson et al., 2018; Richardson & Saxe, 2020b).

2. Materials and methods

2.1. CAToon task

Task creation of the ***C**ognitive and **A**ffective **T**heory of Mind Cart**oon** task* **(CAToon)** included the following steps: (**1**) standardized literature review on ToM fMRI studies (as described in (Fehlbaum, Borbás, Paul, & Raschle, 2020)), (**2**) evaluation for child-appropriateness according to the following requirements: the task should be feasible for young children, including non-readers (no text), has to be engaging and fun, and should ideally be visually entertaining since this has previously been reported to reduce head motion (Huijbers, Van Dijk, Boenniger, Stirnberg, & Breteler, 2017). As a result, we decided on the use of cartoon stories, which are commonly used in the literature, successfully evoke distinct neuronal activation associated with ToM (e.g., (Schlaffke et al., 2015; Sebastian et al., 2012; Völlm et al., 2006; Walter et al., 2009)) and which adhere to the aforementioned requirements. In **Study 1** (behavioral) and **3** (fMRI) these requirements were re-evaluated.

CAToon consists of a total of 30 hand-drawn stories, including two experimental conditions targeting affective ToM (AT) and cognitive ToM (CT) and a control condition (physical causality (PC); **Figure 1**). Each condition comprises 10 stories of similar visual complexity. Ten backgrounds were prepared for the task and each background occurs only once in each condition. The two experimental conditions were designed to differentially motivate affective versus cognitive aspects of ToM reasoning. That means participants should have to infer how a character would react to a fellow character's expressed or expected emotions during AT trials, whereas during CT trials participants should assume how characters would act based on another character's intentions or beliefs. PC trials serve as a control condition, requiring a basic understanding of cause and effect and basic physical laws.

All trials start with three consecutively presented images, followed by a single image displaying three possible endings. CT trial endings consist of one possible, one improbable and one highly improbable/impossible solution. AT trial endings consist of two possible solutions (negative expectancy/positive expectancy) and one impossible solution. In positive expectancy endings a character's emotional needs are met with care or reassurance, whereas in negative expectancy outcomes the character is scolded, ridiculed or ignored. This manipulation allows the investigation of differences in positive or negative outcome expectancy. PC trial endings consist of one possible and two impossible solutions. As physical causality and cognitive ToM conditions have only one correct answer the chance of getting a correct answer is 33% (1/3). For affective ToM (AT) we present two correct (negative and positive expectancy) answers resulting in a higher chance of 66% (2/3). Therefore, for the overall task the chance level is 44%. In other words, in the PC and CT conditions participants have to get at least 3.3 tasks correctly to reach the level of chance (that adds up to 6.6) and in AT condition they have to get 6.6 answers correctly to reach level of chance. Across the 30 trials that adds up to 13.2, which is 44% of 30 tasks.

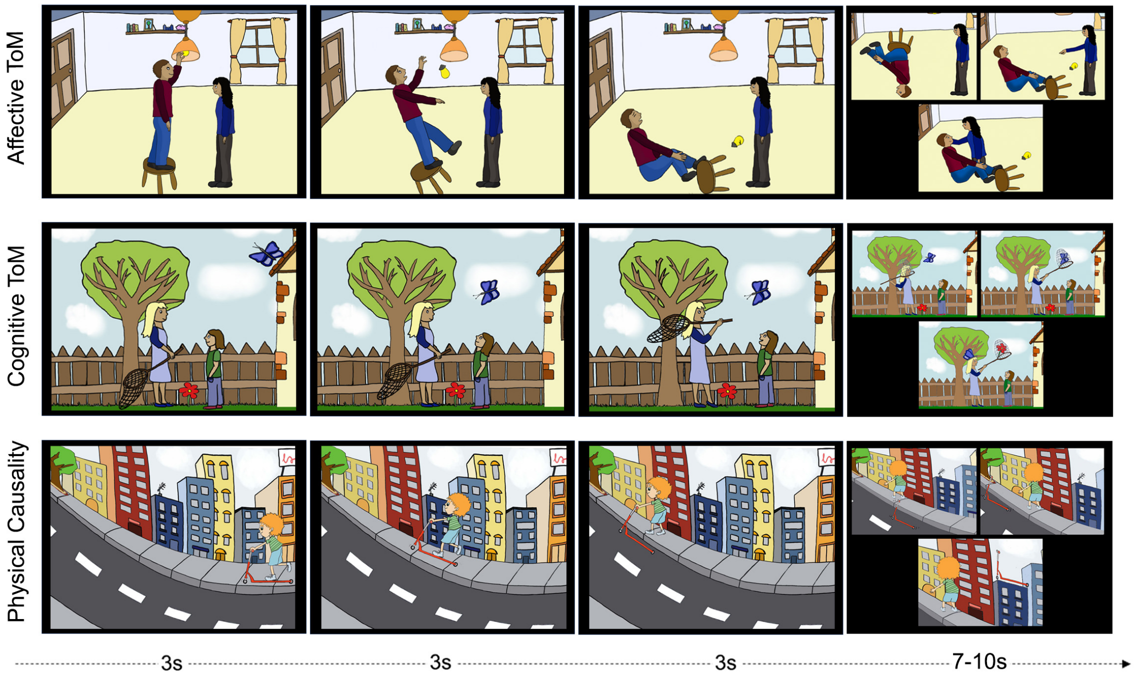


Fig. 1. Three CAToon example trials demonstrating one example of every condition included: affective ToM (experimental condition; top row), cognitive ToM (experimental condition; middle row), and physical causality (control condition; bottom row). The timeline shows the presentation duration for each image presented during fMRI with an answer time window of 7s and 10s for adult and child participants, respectively.

2.1.1. CAToon task evaluation (Study 1: behavioral)

CAToon was evaluated behaviorally in a group setting (first and second grade school classes) or in an individualized manner (preschoolers/kindergarteners). Each participant was asked to look at three images presented in a row and then indicate their choice of the most likely story ending out of three options by either pointing to it (preschoolers/kindergarteners) or by crossing off their choice in a booklet (school-aged children/group setting; details in **Supplement 1)**.

2.1.2. CAToon task evaluation (Studies 2 and 3: fMRI)

A total of 30 cartoon stories were rear-projected onto a screen behind the scanner, viewed by participants via a prism attached to the head coil and displayed using Presentation® software (V16.5, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). Adults completed the fMRI task in one single run (trial order in **Supplement 2**), while children completed the task over the course of two runs (15 trials each) as suggested for fMRI in developmental population (Raschle et al., 2009). Both runs included 5 AT, 5 CT, and 5 PC stories. The run order for children completing the fMRI experiment was alternated (starting with either run1 or run2).

The task had a rapid event-related design with fixed inter-trial intervals of 3s. Before the start of each run, a fixation cross was present for 2s. Each trial started with the consecutive presentation of three images (3s each), followed by a decision phase of 7s for adults. Based on adult feedback from **Study 2** (i.e., challenged by the relatively short answer time), the decision time was extended to 10s for children to assure age appropriateness. Participants had to choose one out of three possible endings through use of a button box (task design in **Figure 1**). Task duration was 8min 36s for adults, and 11min 4s for children (two runs of 5min 32s). Before solving the CAToon neuroimaging task inside the MRI scanner, participants completed three practice trials on a laptop and by use of a cardboard model button box. After these practice trials it was verbally assured that participants understood the task and key points were repeated prior to the start of neuroimaging (further info in **Supplement 2**).

2.2. Participants and analyses

2.2.1. Participants Study 1: CAToon task evaluation in children (behavioral)

For **Study 1** 60 children ages three to nine years (mean age: 5.77 years; 32 boys; group characteristics in **Supplementary Table S1**) completed the CAToon task behaviorally. All children were recruited through daycare, kindergarten or schools. Answer choices, age and gender, but no identifiable personal data, was collected. In line with approval by the local ethics board (Ethikkomission Nordwest- und Zentralschweiz), informed assent to participate was provided by the daycare teachers, school principals or parents. Families were informed about the participation and had the option to withhold contribution.

2.2.2. Analyses Study 1

The mean percentage of correct answers for overall task performance was calculated for each participant. A one-way analysis of variance (ANOVA) was employed to inspect overall performance difference across age groups (by year). The group of nine-year old children was excluded from this analysis due to small sample size (n=2). Prior to conducting the ANOVA, assumption of normality (kurtosis and skewness) and homogeneity of variance (Levene's test) was tested. The results from the ANOVA were followed up with Bonferroni-corrected post-hoc group comparisons. In addition to the categorical investigation of change in performance based on age in years, changes based on age in months were assessed (dimensionally) using partial F-tests to select the best-fitting regression model. Projected changes in performance based on age were calculated using the CurveExpert Professional Software (https://www.curveexpert.net/) by displaying the instantaneous rate of change (the slope of the tangent line at a given point on the curve). All behavioral analyses were performed in SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) or R version 4.0.3 (R Core Team, 2020; https://www.R-project.org/).

2.2.3. Participants Studies 2 & 3: CAToon task evaluation in adults and children (fMRI)

28 healthy young adults and 37 typically developing children took part in the fMRI experiments assessing the neural correlates of mentalizing using CAToon. Participants included in the fMRI studies had normal or corrected-to-normal vision, sufficient German skills, no previous neuropsychological disorder, and average to above average IQ based on their level of education (for adults) or an IQ≥70 (for children; verbal and non-verbal subtests of the German version of the Wechsler Intelligence Scale for Children (WISC-IV; (Daseking, Petermann, & Petermann, 2007)). One adult was excluded from the study due to strong visual prescription glasses that

could not be used or adjusted for within the scanner. Four children were excluded due artefacts caused by braces (n=2), and claustrophobia (n=2). The final sample therefore included 27 adults (20-39 years), and 33 children (7-13 years; group characteristics are listed in **Table 1**).

Adult participants further completed standardized questionnaires assessing callous-unemotional traits (callous-unemotional dimension of the Youth Psychopathic traits Inventory (YPI; (Andershed, Kerr, Stattin, & Levander, 2002)) and empathy (Interpersonal Reactivity Index (IRI; (Davis, 1980)). This allowed the investigation of the association between behavioral scores of callous-unemotional traits or empathy and neural activation during mentalizing using post-hoc assessments. All participants and in case of the children their legal caretakers provided verbal and written consent for taking part in the study.

Table 1. Group characteristics and behavioral scores of adult and child participants of **Studies 2** and **3** (fMRI).

		Adults (n=27;14♂)		**Children (n=33;18♂)**	
		Mean	**SD**	**Mean**	**SD**
Age		25.41	4.16	9.06	2.11
ISCED		4.22	0.97	n.a.	n.a.
IQ	WISC-IV (verbal)	n.a.	n.a.	113.18	17.18
	WISC-IV (matrices)	n.a.	n.a.	110.45	13.83
IRI	Empathic Concern	18.56	4.04	n.a.	n.a.
	Fantasy	16.37	5.06	n.a.	n.a.
	Personal Distress	10.96	4.03	n.a.	n.a.
	Perspective Taking	18.93	3.10	n.a.	n.a.
	Total	64.81	8.91	n.a.	n.a.
YPI	Callous-Unemotional	9.22	1.76	n.a.	n.a.
	Grandiose-Manipulative	8.67	1.95	n.a.	n.a.
	Impulsive-Irresponsible	9.99	2.14	n.a.	n.a.
	Total	9.29	1.48	n.a.	n.a.

Notes. ISCED = International Standard Classification of Education (sum scores), IRI = Interpersonal Reactivity Index (sum scores), YPI = Youth Psychopathic Traits Inventory (mean scores), WISC-IV = Wechsler Intelligence Scale for Children, Fourth Edition, SD = standard deviation, n.a. = not applicable.

2.2.4. fMRI data acquisition (Studies 2 & 3)

For the fMRI task whole-brain T2-weighted echo-planar images were collected on a Siemens 3T Prisma MR scanner using a 20-channel head coil (transverse slice orientation, interleaved acquisition) and the following specifics: field of view=220mm, TR=2000ms, TE=30ms, 42 slices, slice thickness=2mm, voxel size=2.0x2.0x2.0mm, 333 volumes. One additionally structural image was acquired for co-registration during image preprocessing, using the following specifics: voxel size: 1.0×1.0×1.0mm; TR=1900ms; TE=3.42ms; TA=4.26; flip angle=9 degrees; field of view=256x256mm, 192 slices with a slice thickness of 1.00mm. For fMRI acquisition, the first twelve seconds prior to the start of the first stimulus included simultaneous multislice acquisition and dummy scans (discarded), which allowed accounting for T1 equilibration effects. The ToM task lasted 8min and 38s for adults, and 11min and 4s (5min 32s per run) for children. The structural image acquisition lasted 4min and 26s.

2.2.5. Analyses of in-scanner data (Studies 2 & 3)

In-scanner performance (correct versus incorrect answers) and differences between conditions were investigated employing one-way ANOVAs in adults and children. Bonferroni-corrected post-hoc tests were employed to further investigate significant differences between trials.

2.2.6. Whole brain fMRI analyses (Study 2 & 3)

fMRI data was analyzed using the Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/) in MATLAB 2016a (Mathworks, Natick, MA). Regressors of interest were created using a boxcar-function for experimental and control condition and contrasts of interest were calculated for affective ToM (AT>PC), cognitive ToM (CT>PC) and mentalizing (CT|AT>PT). For adults three additional contrasts were calculated. To detect shared activation of affective and cognitive ToM we conducted a conjunction analysis, testing areas activated in both, AT and CT conditions ((CT>PC) & (AT>PC)). Finally, contrasts of distinct activation representing affective ToM (AT>CT) and cognitive ToM (CT>AT) were calculated. For all contrasts the statistical parametric maps were cluster-level FWE-corrected at $p<0.05$, with an initial cluster-building threshold of $p<0.001$, uncorrected. Regressors of interest were implemented for the full trial duration of 16s (adults) or 19s (children), including story presentation and decision time. To assess whether regressor length significantly impacted neural activation, post-hoc analyses were also conducted implementing a reduced regressor (i.e., only considering the story phase of the trials in adults, excluding the decision phase).

Standard fMRI preprocessing included realignment and unwarping, co-registration to each participant's structural image and segmentation prior to normalization into standard space (ICBM152 template). All images were smoothed using an 8-mm full width at half maximum isotropic kernel. Using the art imaging toolbox (https://www.nitrc.org/projects/artifact_detect/) seven additional regressors accounting for motion and variations in mean signal intensity as well as a high-pass filter of 0.01 Hz (128s) were added to the first-level model of each participant.

3. Results

3.1. Study 1: CAToon evaluation in children (behavioral)

3.1.1. Performance across conditions

Summarizing the ratio of correct answers in all children for each condition showed that AT trials were solved correctly in 90.7%, CT trials in 60% and PC trials in 73.3% of all trials. Overall task performance results in a ratio of correct answers ranging from 40-97%. All children reached an accuracy above chance; **Table 2**. Considering only the incorrect solutions within the cognitive ToM conditions, children selected improbable scenarios in 54.9% and highly improbable/impossible solution in 45.1% of the cases. One-way analysis of variance showed a significant effect of condition for correct answers (F(2,177)=43.214, $p<0.001$). Bonferroni post-hoc tests for pairwise comparisons indicated that the ratio of correct answers differed significantly between all three conditions ($p<0.001$). It has to be noted, that a direct comparison may not be warranted and has to be interpreted with great caution, since AT conditions consisted of two possibly correct endings unlike CT and PC trials (one possible ending).

Table 2

Ratio of correct answers (in %) in the different conditions across age groups (in years).

		Age (in years)						
	Overall	3(n=11)	4(n=9)	5(n=8)	6 (n=5)	7(n=11)	8(n=14)	9(n=2)
AT	89.4	76.4	81.1	93.8	88.0	100	98.6	100
CT	57.3	35.5	36.7	65.0	70.0	72.7	73.6	90
PC	71.9	57.3	52.2	78.8	76.0	79.1	87.1	100

Overall	74.6	56.4	56.7	79.1	77.6	83.9	86.4	96.7

Note: AT = affective ToM, CT = cognitive ToM, PC = Physical causality

3.1.2. Performance across age

A one-way ANOVA investigating the effect of age on accuracy rate was conducted after Levene's test indicated equal variances (*F*(5, 52)=0.420, *p*=0.832) and normal distribution within the age groups (**Supplementary Table S2**; (Field, 2013; Ghasemi & Zahediasl, 2012)). The analysis of variances showed a significant effect of age on performance, *F*(5,52)=39.215, *p*<0.001. Bonferroni post-hoc test for pairwise comparisons revealed that 3 and 4-year-olds scored significantly less correct compared to all other age groups, with no further difference between the two youngest age groups (*p*=1.000). Also, while variations in performance remained, no significant differences between 5, 6, 7 and 8-year-olds were observed (**Supplementary Table S3**).

Assessing a dimensional age-performance model revealed a significant improvement of fit comparing the linear and quadratic models (*F*(1)=4.918, *p*=0.031). The age-performance relationship was best described by a quadratic model (**Figure 2**), no further improvement was observed when using a cubic model. The regression model indicates that the instantaneous rate of change (f'(x)) is higher in younger ages and becomes lower in older children. This implicates bigger steps of improvement taking place in younger children. More specifically, in the youngest participants the performance is predicted to improve by 0.97% with each passing month (f'(37)=0.97; equaling one additional correctly solved trial every 3 months). In contrast, the rate of change drops to an improvement of 0.57% at 77 months (f'(77)=0.57), and decreases even further with progressing age (f'(117)=0.17). This means, that the oldest participant within our sample is predicted to improve by one additional correct answer when aging 17 months, reflecting a deceleration of improvement in the older participants.

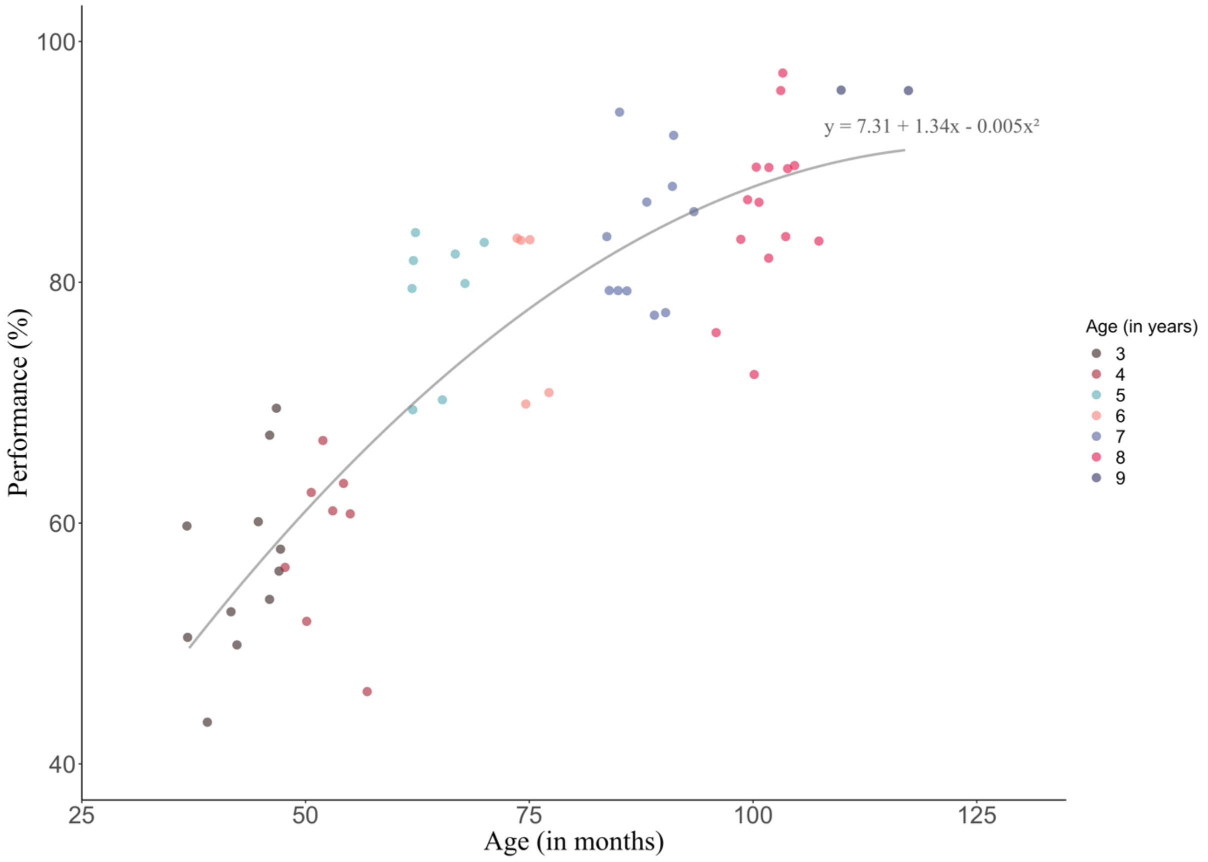


Fig. 2. Scatterplot and quadratic model best representing a performance-age relationship across all children.

3.2. Studies 2 and 3: CAToon task evaluation in adults and children (fMRI)

3.2.1. In-scanner task performance

Overall, adult participants scored above chance with 87.90 % correct answers across the 30 trials (AT: 97.80%, CT:71.90, PC: 94.10), while children scored 81.92% correct across all trials (AT: 95.15%, CT: 72.73%, and PC: 80.91%). The range of correctly answered trials was between 73-100% for adults. Children scored between 63-93% corrects overall. The analysis of variance showed a significant effect of condition on the ratio of correct answers in both, adults (F(2,78)=45.373, p<0.001) and children (F(2,96)=24.35, p<0.001). In adults the ratio of correct answers within CT was significantly lower as compared to AT and PC (both p<0.001), however there was no significant difference between AT and PC trials (p=0.636) according to the Bonferroni post-hoc test for pairwise comparisons. In children, the post-hoc Bonferroni pairwise comparison yielded significant differences between AT and CT (p<0.001), AT and

PC ($p<0.001$), and also PC and CT ($p=0.041$). It has to be noted though, that a direct comparison between AT, CT and PC conditions may not be warranted and has to be interpreted with great caution, since AT conditions consisted of two possibly correct endings unlike CT and PC trials (one possible ending). When looking at the incorrect solutions within the cognitive ToM trials, adults selected improbable scenarios in 87.1% and highly improbable/impossible solutions in 12.9% of the cases. Children selected improbable scenarios in 62.7% and highly improbable/impossible solution in 37.3% of the cases.

3.2.2. Whole brain fMRI analyses

Mentalizing ((*CT* | *AT*)>*PT*) yielded a significant increase in activation in adults and children in frontal brain regions, including medial prefrontal, and orbitofrontal cortices, and inferior frontal gyrus. Activation increase was further observed in temporal regions, such as bilateral temporoparietal junctions, temporal poles and superior temporal sulcus. Parietal regions with heightened activity during mentalizing included inferior parietal lobule, precuneus and supramarginal and angular gyri. Further areas with an increased activation included limbic regions (e.g., cingulate cortex, insula, hippocampus), and basal nuclei (e.g., right thalamus). Affective (AT>PC) and cognitive (CT>PC) ToM-related activation increases were within expected areas, such as medial PFC, temporoparietal junction and precuneus; **see Figure 3, Table 3 & 4**. The repeated analyses of the three main contrasts in the adult group with a shortened regressor including only the story-phase yielded similar activation pattern when compared to analyses implementing the full regressor (data provided through NeuroVault: https://identifiers.org/neurovault.collection:9698).

In addition to parametric correction methods, we also conducted post-hoc non-parametric correction methods in order to test the stability of our findings using different approaches. More specifically, permutation-based multiple comparison correction using SnPM (SnPM13.1.06; http://www.nisox.org/Software/SnPM13/) was computed for the main contrasts of interest (AT > PC, CT > PC, (AT|CT) > PC), employing a cluster-level inference of $p<0.05$ FWE correction after an initial cluster-forming threshold of $p<0.0001$ (as recommended by (http://www.nisox.org/Software/SnPM13/exnew)). Importantly, using non-parametric tests the relevant clusters remained similar (data provided through NeuroVault: https://identifiers.org/neurovault.collection:9699).

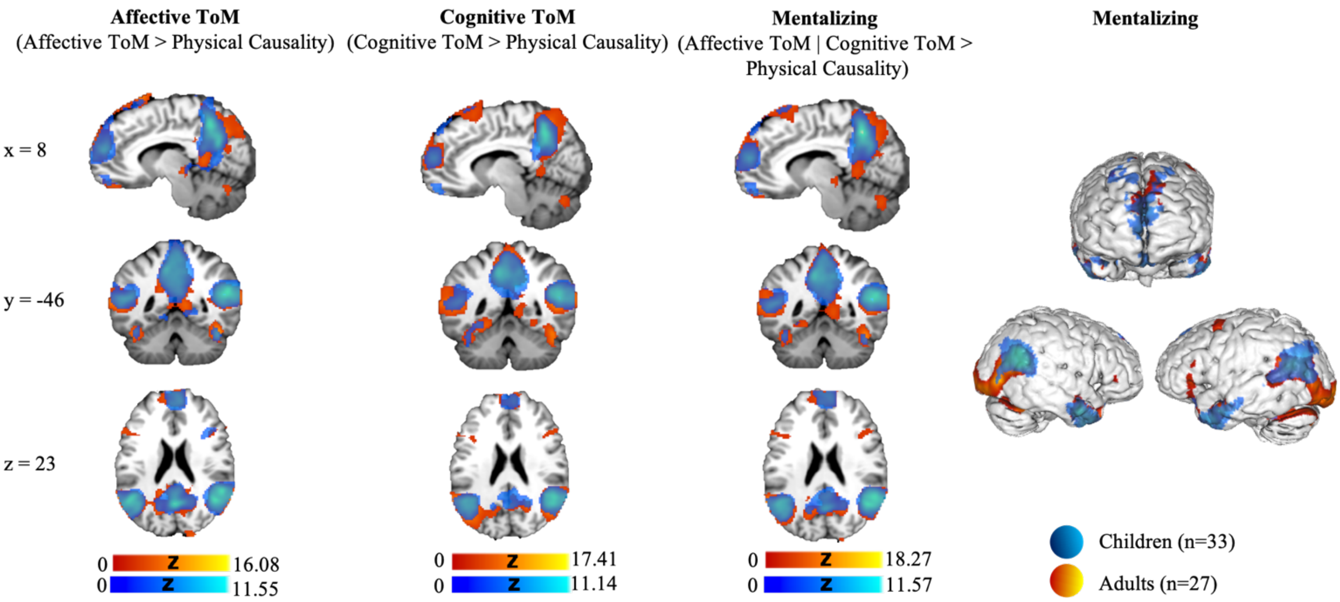


Fig. 3. Statistical parametric maps displaying neural activation during affective ToM, cognitive ToM, and mentalizing in the adult (red) and child (blue) groups (cluster-level FWE-corrected p<0.05, using a cluster-building threshold of p<0.001, uncorrected).

Table 3

Peak activation reports for affective ToM, cognitive ToM and mentalizing in the adult group.

		T	***P*_FWE-corr**	**k**	**MNI**		
Brain region	Hem.				x	y	z
Affective ToM (AT > PC)							
IFG, OFC, temporal pole, inf., mid. and sup. temporal gyri, sup. temporal sulcus, precuneus, fusiform, supramarginal and angular gyri, hippocampus, parahippocampal gyrus amygdala, insula	R/L	16.08	< 0.001	25519	48	-44	18
ACC, medial mid. and sup. frontal gyri, supplementary motor area	R/L	8.39	<0.001	2756	4	56	18
medial OFC	R/L	6.81	0.001	422	4	50	-18
mid. frontal gyrus, precentral gyrus	L	6.68	0.012	345	-40	6	60
IFG (partes opercularis and triangularis)	R	4.75	0.006	249	56	30	4
Cognitive ToM (CT > PC)							
temporal pole, mid., inf.& sup. temporal gyrus, middle frontal gyrus, precuneus, angular gyrus, fusiform gyrus, insula, mid & post. cingulate cortex	R	17.41	<0.001	13605	50	-48	18

temporal pole, inf., med. & sup. temporal gyri,sup. temporal sulcus, supramarginal gyrus, parahippocampal gyrus, IFG, precuneus, fusiform gyrus, insula, amygdala	L	12.42	<0.001	11535	-48	-52	22
mid. & sup. frontal gyri, supplementary motor area, anterior & mid. cingulate cortex, precentral gyri	L	7.01	<0.001	4155	-38	2	48
mid. frontal gyrus, precentral gyrus	R	4.51	0.004	315	34	4	46
Mentalizing: ((CT I AT) > PT)							
temporal pole, inf., mid. and sup. temporal gyri, sup. temporal sulcus, fusiform gyrus, supramarginal & angular gyri, OFC, mid. frontal gyrus	R	18.28	<0.001	9459	50	-46	18
temporal pole, inf. & mid. temporal gyri, inf. parietal lobule, middle & posterior cingulate cortex, precuneus, cuneus, lingual gyrus, fusiform gyrus, OFC, insula	R/L	12.8	<0.001	17954	4	-56	34
medial sup. frontal gyrus, mid. & sup.frontal gyrus, supplementary motor area, anterior cingulate cortex	R/L	8.35	<0.001	4330	6	56	18
hippocampus, lingual gyrus, parahippocampal gyrus, fusiform gyrus, thalamus	R	5.79	0.002	367	20	-36	-12
medial OFC, gyrus rectus	R/L	5.49	0.011	261	4	50	-18
mid.frontal gyrus, precentral gyrus	R	4.96	0.028	212	36	4	46

Note. Hem = hemisphere, ACC = anterior cingulate cortex, IFG = inferior frontal gyrus, OFC = orbitofrontal cortex, inf. = inferior, mid. = middle, sup. = superior, L/R = left/right, T-scores, k = cluster size and xyz co-ordinates of peak voxel according to Montreal Neurological Institute (MNI).

Table 4

Peak activation reports for affective ToM, cognitive ToM and mentalizing in children.

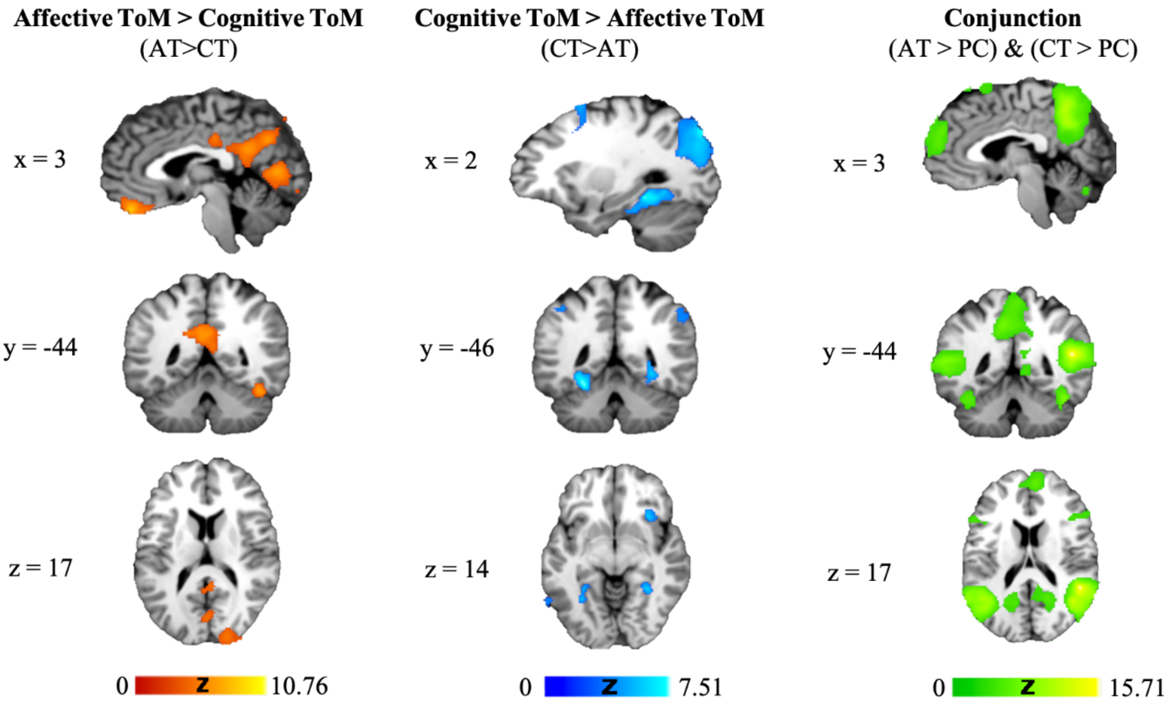
		T	***P*FWE-corr**	**k**		**MNI**	
Brain region	Hem.				x	y	z
Affective ToM (AT > PC)							
temporal pole, paracentral lobule, precuneus, mid. & sup. temporal g., mid. & post. cingulate cortex, hippocampus, supramarginal g., angular g., lingual g., thalamus, amygdala, insula	L/R	11.55	< 0.001	12972	2	-60	24
temporal pole, inf., mid., & sup. temporal g., fusiform g., angular g., lingual g, supramarginal g., parahippocampal g., hippocampus, amygdala, insula	R	10.61	<0.001	7339	46	-56	20
medial OFC, anterior cingulate c., medial sup. frontal gyrus	R/L	8.29	<0.001	2467	-2	50	18
inf. temporal gyrus, fusiform gyrus, parahippocampal gyrus	R	6.93	0.008	340	42	-44	-22
inf., mid. occipital gyrus, lingual gyrus	L	6.13	0.078	184	-20	-100	-8
mid., & sup. frontal gyrus supplementary motor area	R	5.62	0.014	296	12	36	60
precentral gyrus, inf., & mid., frontal gyrus	R	5.39	0.017	284	30	12	26

Cognitive ToM (CT > PC)							
precuneus, mid., & post. cingulate cortex, precuneus, cuneus	R/L	11.14	<0.001	4004	4	-54	40
mid., & sup. temporal g., angular gyrus, supramarginal gyrus	R	9.7	<0.001	2447	50	-56	24
mid. & sup. temporal gyri, parietal inf. lobulus, angular gyrus, supramarginal gyrus	L	8.65	<0.001	2746	-42	-64	28
temporal pole, inf., mid., & sup. temporal gyrus, inferior OFC, insula, fusiform gyrus	L	7.81	<0.001	2107	-62	-8	-20
temporal pole, inf., mid., & sup. temporal gyrus, inferior OFC, insula, fusiform gyrus	R	7.07	<0.001	1380	52	10	-34
Inf. temporal gyrus, amygdala, parahippocampal gyrus, hippocampus, fusiform gyrus, lingual gyurs	L	7.06	<0.001	892	-26	-36	-14
supplementary motor area, superior medial frontal gyrus	R/L	6.79	0.005	443	16	40	56
superior medial frontal gyrus, anterior cingulate cortex	R/L	6.31	<0.001	936	4	58	18
medial OFC	L/R	6.21	0.012	265	4	56	-18
mid., sup. frontal gyrus	L	5.31	0.006	330	-16	36	58
Mentalizing ((CT ∣ AT) > PC)							
precuneus, paracentral lobule, middle & posterior cingulate cortex, cuneus, lingual g.	R/L	11.57	<0.001	5046	6	-52	42
temporal pole, inf., mid., & sup. temporal gyri, angular g., parahippocampal g., hippocampus, amygdala, insula, fusiform g., supramarginal g.	R	10.89	<0.001	5731	46	-56	22
temporal pole, inf., mid., sup. temporal gyrus, parahippocampal gyrus, hippocampus, amygdala, insula, supramarginal g., angular g., lingual g.	L	8.99	<0.001	6475	-40	-68	28
medial sup., & orbitofrontal gyri, anterior cingulate cortex	R/L	7.33	<0.001	2143	8	56	18
supplementary motor area, superior frontal gyrus	R/L	5.86	<0.001	494	16	40	56
inf. temporal gyrus, fusiform gyrus, parahippocampal gyrus	R	5.27	0.006	220	42	-44	-24

Note. Hem = hemisphere, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, g. = gyrus, inf. = inferior, mid. = middle, sup. = superior, L/R = left/right, T-scores, k = cluster size and xyz co-ordinates of peak voxel according to Montreal Neurological Institute (MNI).

Shared and distinct activation for AT and CT: The conjunction of affective and cognitive trials revealed areas of shared activation in bilateral temporal poles and temporoparietal junctions, right superior temporal sulcus, anterior cingulum, precuneus, bilateral inferior frontal gyri and dorsomedial prefrontal cortex (**Figure 4**, **Table 5**). An increase in activation was observed for affective versus cognitive ToM (AT>CT) trials in anterior precuneus, middle and posterior cingulate cortex bilaterally, inferior temporal gyrus, ventromedial prefrontal and orbitofrontal cortices. Significantly greater activation in cognitive versus affective ToM (CT>AT) trials was observed in left middle and superior frontal gyri, right insula, left inferior and middle temporal, bilateral angular and right supramarginal gyri, hippocampus, and posterior precuneus (**Figure 4, Table 5**).

In order to assess whether the analysis timeframe had any effect on the neural activation obtained during cognitive and affective ToM, we re-analyzed contrasts of interest (e.g., 'AT>CT'; 'CT>AT') using a shorter regressor, which resulted in an overall similar activation pattern. However, for the cognitive trials a relative increase in activation in right insular and inferior frontal gyrus was no longer observed employing the shorter regressor (data provided through NeuroVault: https://identifiers.org/neurovault.collection:9698).



Affective ToM > Cognitive ToM
(AT>CT)

Cognitive ToM > Affective ToM
(CT>AT)

Conjunction
(AT > PC) & (CT > PC)

Fig.4. Statistical parametric maps displaying shared (green: (Affective ToM > Physical Causality) & (Cognitive ToM > Physical Causality),) and distinct (red: Affective ToM > Cognitive ToM; blue: Cognitive ToM > Affective ToM) activation in adults. (cluster-level FWE-corrected p<0.05, using a cluster-building threshold of p<0.001, uncorrected)

Table 5
Peak activation reports for distinct (AT>CT), (CT>AT) and shared activation (conjunction analysis in adults ((AT > PC) & (CT > PC)).

		T	***P***	**k**	**MNI**		
Area	Hem.				x	y	z
AT > CT							
precuneus, mid. & post. cingulum, cuneus	L/R	10.76	<0.001	1734	-4	-58	32

gyrus rectus, medial OFC	R/L	8.6	0.001	304	0	42	-22
fusiform gyrus, cuneus, inf, mid. & sup. occipital gyrus, lingual gyrus, inf. & mid. temporal gyrus	R	8.42	<0.001	3595	48	-74	4
inferior temporal gyrus, fusiform gyrus	R	6.62	0.015	178	42	-46	-20
CT > AT							
lingual, fusiform & parahippocampal gyri	L	7.51	<0.001	496	-26	-46	-12
sup. & inf. parietal lobule, angular gyrus, middle occipital gyrus	L	7.48	<0.001	2106	-34	-82	-32
precuneus, superior parietal lobule	R	6.12	0.001	332	18	-70	58
precuneus, lingual gyrus, hippocampus, fusiform & parahippocampal gyri	R	6.01	0.004	263	30	-46	-6
mid. & sup. frontal gyrus	L	5.93	0.001	369	-18	18	42
Insula, inferior frontal gyrus	R	5.6	0.093	125	32	20	-4
angular gyrus, inf. parietal lobule	L	5.07	0.084	129	-40	-48	50
sup. parietal lobule, mid. & sup. occipital gyrus, angular gyrus	R	5.07	0.050	150	36	-80	38
mid. & sup. frontal gyrus, precentral gyrus	R	4.69	0.002	300	24	6	60
inf. & mid. temporal gyrus	L	4.47	0.11	118	-54	-56	-8
supramarginal & angular gyrus	R	4.22	0.002	185	52	-44	36
(AT > PC) & (CT > PC)							
temporal pole, inferior frontal gyrus, fusiform gyrus, inferior, middle & superior temporal gyri, sup. temporal sulcus supramarginal, angular & lingual gyri, insula, parahippocampal gyrus	R	15.72	<0.001	7188	48	-46	18
temporal pole, parancentral lobule, precuneus, supramarginal gyrus, fusiform gyrus, insula, inferior & middle temporal gyrus, mid. & post. cingulum, angular gyrus, lingual gyrus, hippocampus	R/L	11.31	<0.001	13641	4	-52	46
superior medial frontal gyrus, anterior cingulum, middle & superior frontal gyrus	R/L	6.31	<0.001	2565	6	56	18
middle frontal gyrus, precentral gyrus	L	5.52	0.0004	357	-42	2	60
inferior frontal gyrus	R	4.58	0.0003	374	56	30	4

Note. Hem. = hemisphere, OFC = orbitofrontal cortex, inf. = inferior, mid. = middle, sup. = superior, post. = posterior, L/R = left/right, T-scores, k = cluster size and xyz co-ordinates of peak voxel according to Montreal Neurological Institute (MNI).

3.2.3. Post-hoc analyses in adults

Callous-unemotional traits/empathy and neuronal activation during mentalizing: Two post-hoc partial correlation analyses were conducted in the adult group to investigate the association of callous-unemotional traits and empathy with activation in right temporoparietal junction during mentalizing ((AT | CT)>PC). The analyses were controlled for age and gender and Bonferroni correction for multiple comparison testing was used to adjust for the number of tests conducted (*p*<(0.05/2)). Mean parameter estimates from the right temporoparietal junction as defined according Dufour et al. (2013; retrieved from: http://saxelab.mit.edu/use-our-theory-mind-group-maps) and extracted through the MarsBar toolbox [Brett et al., 2002; http://marsbar.sourceforge.net/]. The right temporoparietal junction was chosen as an area of interest because of its key implication across a wide range of mentalizing tasks and studies (Döhnel et al., 2012; Mahy, Moses, & Pfeifer, 2014; Powell et al., 2017; Saxe, 2010). Partial correlation analyses revealed a significant negative correlation between CU-traits and neural activation during mentalizing in right temporoparietal junction (*r*(23) = -0.533, *p*=0.006, but no significant association between empathy levels and activation in right temporoparietal junction (*r*(23)=0.366, *p*=0.072). Further partial correlation tests revealed no significant relationship between callous-unemotional traits and (1) motion during scan (as measured by the average head motion during task or the number of outliers over 1.5mm), and (2) performance on the task, in order to test confounds (**Supplementary Table S5**).

4. Discussion

Here we evaluate feasibility and neural activation patterns evoked by CAToon, a newly developed child-friendly and open-source fMRI Theory of Mind cartoon task. Evaluation included one behavioral study (**Study 1**; behavioral assessment of 60 children; 3-9 years) and two neural evaluations (**Study 2**: fMRI in 27 adults and **Study 3:** fMRI conducted in 33 children). Behavioral results support task feasibility as early as three years of age. However, reliable performance skills are reached around 5 years, which we suggest as an ideal age for fMRI task implementation. fMRI evidence in children and adults confirmed that CAToon is associated with significant activation increases in brain regions associated with mentalizing (e.g., dorsomedial PFC, ventromedial PFC, bilateral temporoparietal junction, middle temporal gyrus, posterior superior temporal sulcus, precuneus, inferior frontal gyrus, precentral gyrus, anterior cingulate cortex and temporal pole). Affective and cognitive ToM trials led to brain activation increases of shared (e.g., bilateral temporal pole, temporoparietal junction, superior temporal sulcus, precuneus and parts of the dorsomedial prefrontal cortex) and distinct brain regions (e.g., AT-specific: orbitofrontal cortex, anterior parts of the precuneus, posterior cingulate cortex, CT-specific: right insula, parahippocampal and fusiform gyrus and posterior potions of the precuneus). Moreover, activation increases in the right temporoparietal junction were negatively correlated with levels of callous-unemotional traits, but not empathy, in adults.

4.1. Feasibility of the CAToon task for children

Behavioral data (**Study 1)** and fMRI data acquisition (**Study 3)** revealed that children of all ages tested were able to complete CAToon above chance level. More specifically, **Study 1** indicated that while all children were able to complete CAToon, children aged five years and up performed significantly better than three and four-year-olds. While children of five years and older still displayed variations in performance, no further significant change in task performance was observed, indicating reliable task performance. Behaviorally, children were most accurate in the affective ToM condition, followed by physical causality and cognitive trials. These findings have to be considered with caution, however, since outcome options were not identical for all conditions (e.g., two possible correct endings for AT compared to CT and PC conditions).

An increasing performance accuracy of children ages five and up as reported here is in line with previous evidence of children performing reliably on explicit ToM tasks starting around four to six years of age (Frith & Frith, 2003; Wellman, Cross, & Watson, 2001). Notably, implicit ToM tasks reveal false belief understanding in infants already (Southgate, Senju, & Csibra, 2007; Surian, Caldi, & Sperber, 2007). However, demands posited by an explicit and/or fMRI task require complementary skills to basic false belief understanding (Lillard & Kavanaugh, 2014). Younger children have been reported to be more challenged by or fail mentalizing tasks that require inhibitory control and working memory (Carlson, Moses, & Breton, 2002; Müller, Liebermann-Finestone, Carpendale, Hammond, & Bibok, 2012; Rakoczy, 2010; Scott & Baillargeon, 2017). The observed performance improvements may result from individual improvements in ToM skills and/or maturation of executive functions typically observed around this age (Roebers, Röthlisberger, Cimeli, Michel, & Neuenschwander, 2011; Röthlisberger, Neuenschwander, Michel, & Roebers, 2010). Such skill improvements have been linked to the start of formal schooling (e.g., (Brod, Bunge, & Shing, 2017; Roebers et al., 2011)). For fMRI purposes we therefore recommend the use of CAToon starting around the age of five years and up, which considers increased challenges posed by an MRI environment (Raschle et al., 2012; Raschle et al., 2009)).

The use of implicit ToM fMRI tasks by passive movie has shown to be possible in children as young as three years of age (Richardson, Lisandrelli, Riobueno-Naylor, & Saxe, 2018). Here we additionally evaluated neural activation associated with the story-phase of the CAToon trials only (as compared to the implementation of regressors that include the story and explicit answer phase) in adults, with comparable outcome. While this may be viewed as a first step towards testing CAToon's suitability as a potential passive viewing task, future investigations in younger children are warranted.

4.2. Neural correlates of mentalizing using CAToon in young adults

Study 2 revealed robust activation increases in brain areas commonly associated with mentalizing for adults, including the dorsomedial and ventromedial PFC, bilateral temporoparietal junction, middle temporal gyrus, posterior superior temporal sulcus, precuneus, inferior frontal gyrus, precentral gyrus, anterior cingulate cortex and temporal poles (Blakemore, 2012; Bzdok et al., 2012; Molenberghs et al., 2016; Van Overwalle & Baetens, 2009). More specifically, the role of the temporoparietal junction during mentalizing is supported by evidence associating this region to temporary mental state attribution of self and others (Mahy et al., 2014; Molenberghs et al., 2016; Van Overwalle & Baetens, 2009). Our findings are further in line with studies demonstrating an involvement of the bilateral temporal pole in context-specific mentalizing (C. D. Frith & Frith, 2006), ventromedial prefrontal cortex in social cognition and self-perception (Amodio & Frith, 2006) and precentral gyrus in the differentiation of self and other (Aichhorn, Perner, Kronbichler, Staffen, & Ladurner, 2006; Ruby & Decety, 2001). Our data supports an involvement of regions specific for affective aspects of mentalizing (e.g., empathic judgment, emotion processing or empathy), including the middle temporal gyrus, ventromedial prefrontal, anterior cingulate and orbitofrontal cortex (Lamm & Singer, 2010; Molenberghs et al., 2016; Northoff & Bermpohl, 2004; Roy, Shohamy, & Wager, 2012; Völlm et al., 2006). Further areas identified, include the insula [recognition and selection of salient events; (Menon & Uddin, 2010)], fusiform gyrus [face processing; (Kanwisher & Yovel, 2006)], right superior temporal sulcus [linked to the observation of socially relevant bodily cues; (Allison, Puce, & McCarthy, 2000; Lee, Gao, & McCarthy, 2012)], precuneus, parahippocampal gyrus and hippocampus [episodic memory retrieval; (Cavanna & Trimble, 2006; Spreng, Mar, & Kim, 2009)].

Through use of conjunction analyses we observed shared and distinct activation patterns when further investigating affective and cognitive ToM trials, which is in line with past evidence (Bodden et al., 2013; Hynes et al., 2006; Schlaffke et al., 2015; Sebastian, Fontaine, et al., 2012). Brain regions that were implicated during both affective and cognitive

ToM included bilateral temporal pole, temporoparietal junction, right superior temporal sulcus, anterior cingulum, precuneus, bilateral inferior frontal gyri and parts of the dorsomedial prefrontal cortex.

Activation was greater for affective as compared to cognitive trials within the anterior part of the precuneus extending into the posterior cingulate cortex, as well as within the cuneus and orbitofrontal cortex. This pattern remained when analyzing only the story portion of the trials, indicating that passive viewing of the CAToon stories may be sufficient to induce affective mentalizing. A distinct activation of the orbitofrontal and ventromedial prefrontal cortex in affective ToM is in line with literature emphasizing its role for affective processing (Hynes et al., 2006; Molenberghs et al., 2016; Schlaffke et al., 2015; Shamay-Tsoory et al., 2010). Similarly, the posterior cingulate, has been linked to empathetic perspective taking (Schlaffke et al., 2015; Völlm et al., 2006). In contrasts to previous findings (Schlaffke et al., 2015), we have not detected distinct activation in basal ganglia for affective compared to cognitive ToM. This may result from different task designs, as Schlaffke et al., (2015) measured affective and cognitive ToM through the use of the same set of images, but different questions, while CAToon included distinct trials for each condition.

Areas with increased activation during cognitive versus affective trials included posterior parts of the precuneus, parahippocampal gyrus, hippocampus and right insula. However, removing the explicit decision phase from the model, the right insula and inferior frontal gyrus did not remain significant. Both regions have been linked to decision making processes (Hartwright, Hansen, & Apperly, 2016; Paulus, Feinstein, Leland, & Simmons, 2005), which may explain why a shortened model, excluding the decision phase, no longer results in activation increases of these areas.

4.3. Callous-unemotional traits, empathy and mentalizing

We observed a negative association between callous-unemotional traits and neural activation within the right temporoparietal junction in adults. The right temporoparietal junction is most commonly implicated when inferring about thoughts, beliefs and emotional states (Molenberghs et al., 2016). Within the limited literature investigating the relationship between callous-unemotional traits and neural correlates of mentalizing, our findings support those establishing a negative link (Lockwood et al., 2013; Sebastian, McCrory, et al., 2012) between callous-unemotional traits and mentalizing skills. They may thus be in line with evidence suggesting that adults with higher levels of callous-unemotional traits are more likely to disregard others' feelings (Scheepers, Buitelaar, & Matthys, 2011) or more likely to display deficient affective perspective taking (Lui, Barry, & Sacco, 2016). However, past findings are inconclusive, with some reporting a positive association (Gao et al., 2019) or those missing to find a significant connection (O'Nions et al., 2014). Notably, levels of callous-unemotional traits displayed within our adult group did not correlate with an increase in motion during fMRI task performance.

4.4. Neural correlates of mentalizing using CAToon in children

After successfully evaluating the neural correlates associated with CAToon task performance in adults (**Study 2**), **Study 3** further assessed the neural correlates in a group of children (ages 7-13 years), thus testing feasibility in an initial fMRI study of children using CAToon. We observed activation of the mentalizing network comparable to findings in our adult study. Activation clusters in the child group were similar, though seemed slightly less pronounced as reported in adults, which is in line with studies investigating adult and developmental populations during mentalizing (Fehlbaum et al., 2020; Richardson et al., 2018). An increase in neural activation was observed in areas including bilateral temporoparietal junction, medial prefrontal cortex and precuneus (in line with (Gweon et al., 2012; Richardson & Saxe, 2020b)). Our findings provide first evidence for the feasibility of employing CAToon as an fMRI task in children. An effort in developing and subsequently sharing age-appropriate neuroimaging tasks may further replicability and reproducibility of findings (Klapwijk, van den Bos, Tamnes, Mills, & Raschle, 2019). To provide opportunity for others using CAToon or our findings further, the task and all T-maps reported in the manuscript are made openly available at https://www.jacobscenter.uzh.ch/en/research/developmental_neuroscience/downloads/catoon.html.

CAToon adds to previous tasks used in children by measuring affective and cognitive aspects of mentalizing. However, it has to be highlighted that the two conditions are not as well isolated (e.g., Sebastian et al., 2012 had distinct cognitive and affective trials) or matched (e.g., Schlaffke et al., 2015 implementing the same images for cognitive and affective trials, but different questions asked), since for CAToon cognitive and affective ToM both include people and affective elements. While naturalistic (e.g., cognitive and affective ToM are social processes, rarely isolated from humans or fully free of affect in real life), this implementation results in a certain confound rendering it challenging to fully isolate individual aspects. Future studies could further test individual stimuli ratings by content, which may then be associated with neural activation in each condition to test the influence of different stimulus characteristics. CAToon was employed as an explicit task, including in-scanner responses. However, first analyses reveal its potential as a passive viewing task, which might be more appropriate for very young participants.

4.5. Study limitations

Several limitations have to be noted. In **Study 1** (behavioral evaluation in children), CAToon was presented either in a one-on-one setting or, for older children, in groups. This procedure ensured appropriate understanding and task conduction for younger children, but limits comparability across all age groups. It is notable that younger children performed still lower than children ages five and up. It is also mentionable that there was no strict timing or time limit for the image presentation and decision phase within the behavioral study, which is not possible when running CAToon within an fMRI setting.

Additionally, since characters' emotional expressions were included in cognitive ToM scenarios, the affective and cognitive scenarios presented in CAToon are less clearly distinct as compared to previous paradigms (e.g., Sebastian et al., 2012). While the correct solving of the CT and AT trials is designed to rely on the inference about the targeted mental states (i.e., intentions in cognitive and emotions in affective trials), a direct investigation about the cognitive process underlying participants' answers (i.e., understanding what inferences they make during certain trials) should be investigated in future studies (e.g., collecting subjective responses of participants' reasoning for the answer selection). However, neural activation in adults provides initial evidence of the conditions eliciting activation in established areas (e.g., increased recruitment of ventromedial prefrontal and orbitofrontal cortex during affective trials)."

A deliberate choice to include two correct answers within the affective trials was made in order to be able to investigate positive/negative expectancy in later studies (e.g., of children with and without disruptive behaviors or prior maltreatment). This might be considered as a caveat as it makes the direct comparison of behavioral performance between the different trial types challenging. From a neural perspective, it might be hypothesized that the inclusion of two possible correct answers may require children to evaluate their response even more, thus increasing the need for mentalizing. However, such an effect will have to be further evaluated.

We would also like to note, that while there are variations in behavioral task performance across all ages, there are no significant improvements after the age of 5 years when measured outside the fMRI environment (**Study 1**), or after the age of 7 years when using CAToon inside the fMRI environment (**Study 3**). In future studies, the use of an additional, established behavioral measure is recommended in order to establish whether children's performance and neural activation is clearly associated. Also, CAToon task stimuli were not tested in different cultures, limiting generalizability and highlighting opportunities for future investigation. Due to the small sample size for brain-behavioral correlations (e.g., comparison of neural activation with callous-unemotional traits/empathy) such findings must be interpreted with caution (Cremers, Wager, & Yarkoni, 2017).

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Declaration of Competing Interest

The authors report no declarations of interest.

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Supplementary material is available at Developmental Cognitive Neuroscience online.

4. Study III

Mental well-being during the first months of Covid-19 in adults and children: behavioral evidence and neural precursors

Réka Borbás[1,2], *Lynn V. Fehlbaum*[1,2], *Plamina Dimanova*[1], *Alessia Negri*[1], *Janani Arudchelvam, Cilly Bernardette Schnider, Nora M. Raschle*[1,2]

[1] *Jacobs Center for Productive Youth Development at the University of Zurich, Zurich, Switzerland*

[2] *University of Basel, University Psychiatric Clinics Basel, and University Hospital Basel, Basel, Switzerland*

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Abstract

Pandemics such as the Covid-19 pandemic have shown to impact our physical and mental well-being, with particular challenges for children and families. We describe data from 43 adults (31♀, ages = 22–51; 21 mothers) and 26 children (10♀, ages = 7–17 years) including pre-pandemic brain function and seven assessment points during the first months of the pandemic. We investigated (1) changes in child and adult well-being, (2) mother–child associations of mental well-being, and (3) associations between pre-pandemic brain activation during mentalizing and later fears or burden. In adults the prevalence of clinically significant anxiety-levels was 34.88% and subthreshold depression 32.56%. Caregiver burden in parents was moderately elevated. Overall, scores of depression, anxiety, and caregiver burden decreased across the 11 weeks after Covid-19-onset. Children's behavioral and emotional problems during Covid-19 did not significantly differ from pre-pandemic levels and decreased during restrictions. Mothers' subjective burden of care was associated with children's emotional and behavioral problems, while depression levels in mothers were related to children's mood. Furthermore, meeting friends was a significant predictor of children's mood during early restrictions. Pre-pandemic neural correlates of mentalizing in prefrontal regions preceded later development of fear of illnesses and viruses in all participants, while temporoparietal activation preceded higher subjective burden in mothers.

Introduction

The global onset of the coronavirus disease 2019 (Covid-19) pandemic has been recognized as a significant threat to our physical and mental well-being. Worldwide efforts have been implemented including protective health measures to slow down or prevent the direct physical effects of the virus. In Switzerland these restrictions included school closure, work-from-home orders, and travel restrictions. Past and accumulating evidence indicates that restrictions (e.g., school closure, lockdown, social distancing) may have a significant effect on individuals' psychosocial functioning, possibly through increases in emotional distress[1,2]. Evidence indicates that mental health consequences include an increase in neuropsychiatric symptoms of affect and behavior[3,4]. Such increases in negative effects (e.g., stress, anxiety, depression, or somatic complaints) associated with Covid-19 and restrictions are reported globally[1,2,5,6]. The duration of lockdown and restrictions have been linked to increased distress[5]. Negative effects tend to be higher in younger individuals, those with chronic disease or pre-existing health conditions, females and those living alone or in socioeconomic adversity[1,2,7].

Children's, parents', and families' lives may be particularly impacted by Covid-19-related restrictions[8]. A sudden decrease in social contacts is opposite to the human social nature and our existing routines[9,10]. For children and adolescents, positive peer-relationships, the ability to pursue hobbies and educational opportunities are affected[11]. For parents, an increased burden may result from a disrupted work-life balance. Parental exhaustion, irritability, and mental health symptoms (e.g., depression and anxiety) have been reported to increase during pandemics[12,13]. Moreover, parents' psychological distress can affect children's ability to adjust to novel situations and may therefore promote the development of behavioral and emotional problems[14]. High anxiety or depressive symptoms in parents have been associated with an increase in harsh parenting and child abuse potential[15], indicating urgent consideration for policymakers to provide resources and support for at-risk families.

Notably, reports on increases in emotional distress are complemented by reports of a smaller, but significant, proportion of individuals who describe no changes or increases in well-being during restrictions. Such data indicates that interindividual differences in the effect of restrictions on mental health should be considered[2]. For example, restrictions may bring some families closer together, increase parent–child bonding and joint experiences[7]. An increased understanding of interindividual differences that protect or increase risk for psychopathologies holds the potential to inform personalized support associated with pandemics.

The identification of potential precursors for psychosocial functioning during challenging life events is crucial for the development and implementation of prevention and intervention measures. Socioemotional abilities represent different skill sets of social and emotional functioning[16] which may serve as potential antecedents of psychosocial functioning during challenging life events[17]. Successful socioemotional skill development in children is positively linked to present and future well-being[18] and a disruption of these has been linked to externalizing and internalizing problems[19]. Furthermore, socioemotional skill development strongly relies on caregiver-child relationships and dyadic learning[20].

A fundamental ability for many later-emerging socioemotional abilities is mentalizing, a sociocognitive skill enabling the understanding of emotions, thoughts or motives of others and oneself (enabled by our so-called Theory of Mind and impacted by parenting behaviors[21]). Having a well-developed Theory of Mind has been associated with higher social competences, psychological and physiological functioning[22]. Contrariwise, impaired mentalizing abilities have been linked to stress and depression[23], potentially serving as a predictor of these[17]. On a neural level, the functional brain network associated with mentalizing typically includes areas such as the bilateral temporoparietal junction, precuneus, medial prefrontal cortex and right superior temporal sulcus[24], with the temporoparietal junction and prefrontal cortex particularly relevant when thinking about others' and one's own mental states[10]. The right temporoparietal junction has been the area most consistently activated during different types of fMRI mentalizing tasks[24]. The right dorsolateral prefrontal cortex is similarly involved during mentalization and perspective taking, but also plays a key role in emotion regulation, which is strongly associated with mental well-being[25,26]. A disrupted ability to mentalize, including associated neural alterations, can be found in clinical disorders, such as borderline personality disorder, conduct disorder or alexithymia[27,28].

Increasing evidence highlights the urgent need to consider the indirect consequences of the pandemic on physical and psychological well-being. Children's, parents', or families' lives may be particularly affected, and parental well-being is suggested to be intertwined with that of children. Past evidence further indicates that well-being and stress are moderated by sociocognitive skills. In this study, we aimed (1) to investigate the effects of Covid-19 and associated restrictions on child and adult well-being as measured repeatedly during the first months after Covid-19 onset; (2) to assess associations of mental well-being (e.g., anxiety, depression, caregiver burden) in mothers with children's emotional and behavioral problems or mood; (3) to examine the association between the neural correlates of mentalizing as measured prior to Covid-19 and later development of fear of contamination and illnesses in all participants, or caregiver burden in mothers. In line with prior work[2,29], we expect reports of negative effects on mental well-being (e.g., general health, anxiety, distress, depression), with possible changes over time. Emotional and behavioral problems in children may vary over time. Furthermore, we suggest that variations in emotional and behavioral problems or mood in children are positively associated with variables of mental well-being of their mothers. In everyday life, increased mentalizing skills are linked to improved socioemotional functioning[22]. However, studies have shown that particularly during challenging life circumstances an elevated tendency to mentalize may also be negatively associated with our well-being (e.g., higher anxiety in those with better mentalization skills[17]). In line with this observation, we suggest that neural correlates of mentalizing are positively associated with later caregiver burden or the development of higher anxiety and fears associated with viruses.

Methods

Participants

Ninety-eight European participants (60 adults and 38 children) of a previous cross-sectional neuroimaging study investigating socioemotional development between 2018 and 2020 were asked to participate in the Covid-19 online follow-up assessments. Pre-pandemic assessments included behavioral tests and functional magnetic resonance imaging (fMRI) during mentalizing; see study description in[30]. We here describe data from the first 3 months after the first implementation of stringent restrictions following Covid-19 onset in Switzerland and include seven assessments time points across this time period (Fig. 1). Sixty-nine participants (43 adults: 31 females; average age = 35.14 years; age range 22–51 years; 26 children: 10 females; average age = 10.69 years; age range 7–17 years) agreed to take part in the follow-up study; retention rate per time point for these 69 individuals were as follows: **T3** (41 adults [95.35%], 24 children [92.31%],); **T4** (39 adults [90.70%], 23 children [88.46%],); **T_E** (40 adults [93.02%], 24 children [92.31%]); **T5** (29 adults [67.44%], 15 children [57.69%]); **T6** (37 adults [86.05%], 23 children [88.46%]).

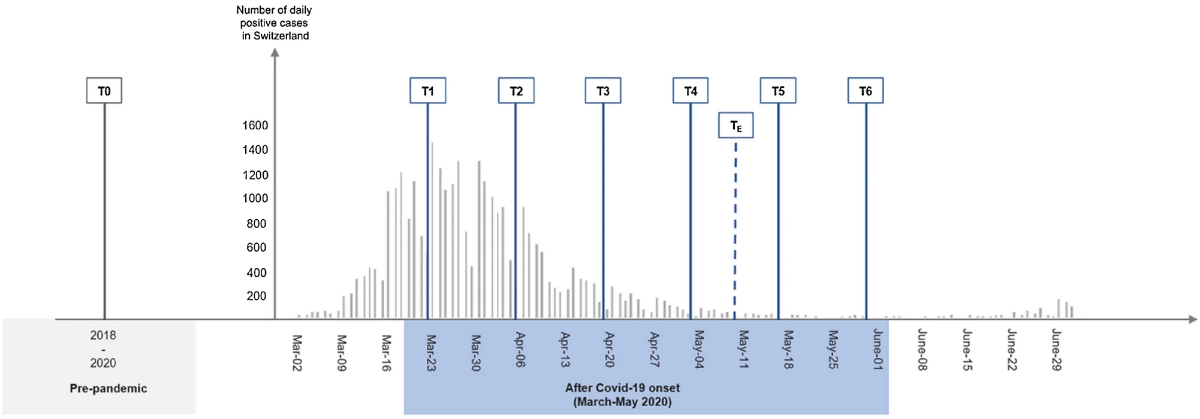

Figure 1. Study design and overview of assessments conducted prior to (T0) and during restrictive measures (T1-T6).

All adults and children were previously recruited from the general community and schools for a study on the behavioral and neural correlates of socioemotional skill development. More specifically, participants took part in an evaluation study for a novel cognitive and affective Theory of Mind cartoon task (specifics may be found in[30]). Furthermore, 21 women and 26 children were related (mother–child dyads). Parents of the children reported no known clinical diagnosis for 23 of the children, for three children a clinical diagnosis of ADHD was indicated and for one of these three children the parents further noted a possible developmental delay. In line with guidelines and approval by the local ethics board (Ethikkomission Nordwest- und Zentralschweiz) all participants signed an informed consent form. Additionally, in case of children, verbal assent of the child and written informed consent from a parent and/or legal guardian was collected. All research presented here was performed in accordance with the relevant guidelines and regulations of the Ethikkomission Nordwest- und Zentralschweiz.

Assessments

Overall, eight testing time points are included, with the first (T0) reporting data obtained during the two years prior to the pandemic. Seven assessments were conducted across 75 days (11 weeks) after Covid-19 onset in Switzerland. The online assessment started following nationwide restrictions implemented in Switzerland on March 16th, 2020, including the ban of events, school closure, closure of all non-essential and hardware stores, garden centers, markets, museums, zoos, nightclubs, closure of hairdresser, restaurants, ban of gatherings (maximum of five people) and home-office orders, etc. Schools were re-opened on May 11th, 2020, resulting in more parents returning to work. Only assessments relevant to the present analyses are described below. Further details, including information for all assessments conducted prior to Covid-19 onset (T0) and during restrictions (T1–T6) may be found in the Supplementary Methods.

Testing prior to Covid-19 (T0) took place between March 2018 and February 2020 and included functional neuroimaging during mentalizing. Online assessments after Covid-19 onset were conducted from March to May 2020. Participants filled out six biweekly online questionnaires (labelled as T1, T2, T3, T4, T5, T6 in Fig. 1). For adults, these targeted *anxiety* (State-Trait Anxiety Inventory or STAI-6; a self-report questionnaire to assess anxiety level as state[31]), *depression* (Center for Epidemiologic Studies Depression Scale or CESD-R, German version[32]; assessing symptoms in the last 1–2 weeks relating dysphoria, anhedonia, appetite, sleep, thinking, guilt, fatigue, movement and suicidal ideation), *general health* (General Health Questionnaire or GHQ-12, German version; a self-report instrument to screen for psychosocial well-being[33]), *distress* (questionnaire adapted from the Kessler Psychological Distress Scale, but answer format was modified allowing participants to indicate their emotional state in relation to their usual emotional state[34]) and *subjective burden of caregiving* for mothers (the Burden Scale for Family Caregivers or BSFC-s[35]; a self-report questionnaire assessing subjective burden of family caregivers, which was adapted to capture increased burden in parental responsibilities during restrictions). In children *emotional and behavioral problems* were assessed using the Strengths and Difficulties Questionnaire (SDQ[36]) and subjective mood ratings (children had to choose between 5 different smileys in order to indicate their mood in the last days. Ratings included 1: very happy, 2: happy, 3: unsure, 4: unhappy, 5: very sad). Children were further asked whether they had met any friends in the previous week. *News consumption* (adults only) and *time spent outside* (all participants) were assessed by asking participants to indicate the amount of time spent on these activities on a 5-point Likert scale. Adults reported their daily news consumption across all forms of media through the following scale: 1: no time, 2: approximately 15 min, 3: approximately 30 min, 4: approximately 1 h, 5: more than an hour of time spent consuming news). Adults and children indicated the average duration of spending time outside per day in the past week (1: no time, 2: half an hour, 3: 1 h, 4: 1–2 h, 5: more than 2 h of time spent outside).

One extra questionnaire (T_E, between T4 and T5) was added before a first ease in restrictions was introduced by the government. This extra testing consisted of the Child Behavior Checklist (CBCL[37]) evaluating *child behavior* and the *Fear of Illness and Virus Evaluation* (developed by Professor Jill Ehrenreich-May, https://adaa.org/node/5168). CBCL was also acquired at T0 allowing a pre-/post-comparison. Of the six biweekly assessments, the last two (T5, T6) were conducted after schools reopened.

Behavioral data analyses

Mental well-being during Covid-19-related restrictions

First, adults' scores in anxiety depression, and caregiver burden were screened. STAI-6 total scores above 40 were considered as an indicator of clinically significant levels of anxiety, according to[38]. Depression scores were screened to detect subthreshold depression symptoms according to the CESD total score ($CESD_{total} \geq 16$) or meeting criteria for a major depressive episode (description of the algorithm for calculation may be found at: https://cesd-r.com/cesdr/). Next, we calculated the 11-week prevalence of clinically significant anxiety, subthreshold depression and major depression (i.e., the proportion of participants surpassing relevant cut-off scores and fulfilling criteria at least once during the assessment period). Finally, parental burden was classified as "low", "moderate" or "high" according to the classification suggested by Pendergrass and colleagues[39] (BSFC-s scores of 0–4 are considered as low; 5–14 as moderate; 15–30 as high).

We investigated the effect of Covid-19 and related restrictions on mental well-being using linear mixed-effect models in R (https://www.r-project.org/). As a first step, missing data points were evaluated to assess whether these were missing at random (MAR). In case of no violation of MAR assumption missing data was replaced by Multivariate Imputation by Chained Equations MICE package in R[40] employing the predictive mean matching method. Overall, 14.41% of the testing time points reported in the present analyses were imputed (12.79% in adults, 16.03% in children).

Linear mixed-effects models were employed to analyze the relationship between length since Covid-19 onset and continuous outcome measures (depression, anxiety, general health, distress, caregiver burden, and emotional and behavioral problems in children) using lme4[41]. Duration (in weeks) was entered as a fixed effect. Subjects were entered as a random effect and the model allowed for random intercepts and random slopes accounting for non-independence of datapoints (same person answering multiple times). Furthermore, a different response of the subjects was expected (each person might react differently to duration of restrictions). *P* values were obtained by the Satterthwaite approximation as recommended by Luke et al.[42] for small group sizes using the lmerTest package[43]. This pipeline was adjusted for the analysis of depression, caregiver burden and emotional and behavioral problems in children for the following reasons: Depression scores (CESD-R) and children's emotional problems, conduct problems, hyperactivity, peer problems and total scores (SDQ) were log-transformed after a visual inspection of the data revealing a right skew. For caregiving burden (BSFC-s), and children's peer problems and total score of emotional and behavioral problems (SDQ), the full model (including random intercepts and slopes for each subject) indicated an overfit. Consequently, a simplified model excluding random slopes by subject was implemented.

For the analysis of categorical, non-parametric data (i.e., clinically relevant threshold for depression reached [yes/no], time spent outside, news consumption and mood in children), Friedman tests were used. Significant main effects were followed up using post-hoc pairwise comparisons and adjusted using Holm-Bonferroni correction. Finally, one-way analysis of variance was employed to test whether emotional and behavioral problems (SDQ and CBCL) in children differed prior to and during Covid-19-related restrictions. For the score during Covid-19 all time points of SDQ were averaged to build one score (average of five online assessments). CBCL was only assessed once at T_E.

Mother-child associations

To test whether mental well-being in mothers (anxiety, depression, and caregiver burden) explained variability in children's emotional or behavioral problems a multiple regression analysis was implemented corrected for children's age and sex. Since emotional and behavioral problems in children were assessed through parental reports, parental bias may impact findings. Therefore, we repeated the multiple regression analysis by using mood scores provided by the children as a dependent variable.

Post-hoc follow-up assessment

Mental well-being and the development of negative symptoms during stressful life events have been suggested to be influenced by further variables of interest, including sex and parenting[44], news exposure[2] or time spent outside[45]. For adult participants, multiple regression analysis controlling for age was conducted to assess whether variation in mental well-being (i.e., anxiety, depression, or distress) were explained by sex, news consumption, time spent outside or parenthood. For children, we assessed whether children's well-being (self-report for mood) during restrictions was explained by time spent outside or meeting friends (yes/no) using multiple regression analyses, controlling for age and sex of the children.

Children's subjective reports

Children were asked two open-ended questions: At T1–T4, these were "What do you like about spending more time at home now?" and "What do you like less about spending more time at home now?”. At T5 (after the first week of school opening) and T6 (3 weeks after school reopened) these were changed to “What do you like about going back to school?” and “What do you like less or think, is a bit annoying, about going back to school?” Subcategories based on topics mentioned were built and coded by two independent reviewers (Supplementary Methods).

fMRI data analyses

fMRI data was analyzed using SPM12 running on MATLAB R2020b (www.fil.ion.ucl.ac.uk/spm). Neural correlates of mentalizing were tested using the CAToon task[30] (see[30] and Supplementary Methods). fMRI was acquired for all participants between 2018 and 2020. In short, fMRI during mentalization was acquired using a cartoon-based Theory of Mind task [experimental condition: affective (AT) and cognitive (CT) Theory of Mind; control condition: physical causality (PC)]. The neural correlates of mentalizing were based on a regressor of interest including both cognitive and affective Theory of Mind as compared to physical causality ((AT|CT) > PC). Whole-brain T2-weighted echo-planar images were collected using a 20-channel head coil on a Siemens 3T Prisma MR scanner (specifics in Supplementary Methods). Group analyses included age and sex as covariates and all findings were corrected for multiple comparisons using whole brain family-wise error correction (FWE).

For the present purpose mean parameter estimates were extracted for areas of interest consistently recruited during mentalizing[24], including right temporoparietal junction (TPJ) and dorsolateral prefrontal cortex (dlPFC), using the MarsBar toolbox[46]. More specifically, right TPJ was selected as a region of interest since it is most consistently recruited during mentalizing tasks and perspective taking in both children and adults[47]. A 7 mm sphere was extracted for the right TPJ, because the group activation cluster extended beyond the area of interest (spanning over 5860 voxels reaching from temporal pole to occipital areas). The right dlPFC was selected as a region of interest, because of its involvement during mentalization and perspective taking, but also because of its key role in emotion regulation, which is in turn strongly associated with mental well-being[25], including the development of stress-related burden, depression and anxiety[26,48]. To test whether these regions were significant predictors of fears about contamination and illness, or caregiver burden, we employed multiple regression analyses controlling for age and sex when applicable. For the multiple regression analysis including caregiver burden we calculated one score averaging all $\text{BSFC}_{\text{total}}$ scores. In-scanner data collection was only evaluated to assure task compliance (i.e., no more than 10% missing in all trials; Supplementary Table S1).

Results

Behavioral findings

Descriptive statistics

A summary of the behavioral data collected prior to and during the early weeks following Covid-19 onset is included in Table 1 (in children scores prior to and scores averaged over the 11-weeks online assessment are reported. For adults only averaged scores are reported; Fig. 2).

Table 1. Group characteristics of adults and children prior to and during the first months after Covid-19 onset.

	Adults (n=43, 31 females)			**Children (n=26, 10 females)**				
	First pandemic months	M ± SD		Pre-pandemic	M ± SD		First pandemic months	M ± SD
Age	in years	35.14 ± 9.20	**Age**	in years	9.58 ± 2.39	**Age**	in years	10.69 ± 2.52
Time s. 1st test	in months	18.76 ± 7.03	**IQ**	Verbal	13.88 ± 8.94	**Time s. 1st test**	in months	13.64 ± 7.01
ISCED		4.84 ± 1.75		non-verbal	12.88 ± 4.48	**SDQ [a]**	emotional problems	1.21 ± 1.62
BSFC [ab]	subjective burden of care	8.32 ± 4.42	**SDQ**	emotional problems	1.73 ± 2.24		conduct problems	1.64 ± 1.49
STAI-6 [a]	anxiety	38.85 ± 8.57		conduct problems	1.69 ± 1.72		hyperactivity	2.88 ± 1.93
Distress [ac]	distress	4.09 ± 0.56		hyperactivity	2.81 ± 1.86		peer problems	1.64 ± 1.44
GHQ [a]	mental health	5.15 ± 2.57		peer problems	0.92 ± 1.41		prosocial	6.56 ± 1.53
CESD-R [b]	depression	9.96 ± 10.60		prosocial	7.35 ± 1.67		total	7.38 ± 4.87
				total	7.15 ± 4.97	**CBCL**	withdrawn	54.58 ± 5.38
News	[1] no time	1.89%	**CBCL [d]**	withdrawn	54.27 ± 5.50		somatic problems	56.54 ± 7.46
consumption [a]	[2] 15 minutes	36.04%		somatic problems	55.46 ± 5.57		anxious/depressed	55 ± 8.32
(daily)	[3] 30 minutes	30.76%		anxious/depressed	56.73 ± 8.49		social problems	53.13 ± 4.78
	[4] 1 hour	21.82%		social problems	53.65 ± 4.63		schizoid-compulsive	54.13 ± 6.49
	[5] > 1 hour	9.49%		schizoid-compulsive	54.35 ± 6.36		attention problems	55 ± 5.82
				attention problems	55.19 ± 5.84		delinquent behaviour	52.38 ± 4.43
Time outside[a]	[1] no time	1.25%		delinquent behaviour	52.69 ± 3.90		aggressive behaviour	53.29 ± 5.29
(daily)	[2] 30 minutes	21.78%		aggressive behaviour	55.38 ± 6.83		total	51 ± 9.36
	[3] 1 hour	19.77%		Total	53.81 ± 8.45	**FIVE**	fears about contamination and illness	12.38 ± 2.78
	[4] 1 to 2 hours	34.93%					fears about social distancing	15.17 ± 4.27
	[5] > 2 hours	22.28%					behaviors related to illness and viruses	29.63 ± 5.32
FIVE	fears about contamination and illness	13.53 ± 2.94					impact of illness and virus fears	2.83± 1.01
	fears about social distancing	15.10 ± 3.63					total	30.38± 6.76
	behaviors related to illness and viruses	30.55 ± 4.85				**Time outside[a]**	[1] no time	0.72%
	impact of illness and virus fears	2.98 ± 1.05				**(daily)**	[2] 30 minutes	12.79%
	total	31.6 ± 6.11					[3] 1 hour	18.49%
							[4] 1 to 2 hours	32.90%
							[5] > 2 hours	35.10%
						Mood[a]	[1] very happy	31.34%
							[2] happy	46.07%
							[3] unsure	15.44%
							[4] unhappy	5.70%
							[5] very sad	1.45%

[a]average score; [b]in mothers only; [c]Distress: 1 - much less than usual, 2 - quite less than usual, 3 - a little less than usual, 4 - as much as usual, 5 - a little more than usual, 6 - quite a bit more than usual, 7 - much more than usual; [d]N=25 (out of a total N pre-/during confinement of 26); Time s. 1st test=time since first testing; ISCED=International Standard Classification of Education; BSFC=Burden Scale for Family Caregivers; STAI-6=State-Trait Anxiety Inventory; GHQ=General Health Questionnaire; CESD-R=Center for Epidemiologic Studies Depression Scale; FIVE=Fear of Illness and Virus Evaluation; SDQ=Strengths and Difficulties Questionnaire; CBCL=Child Behavior Checklist

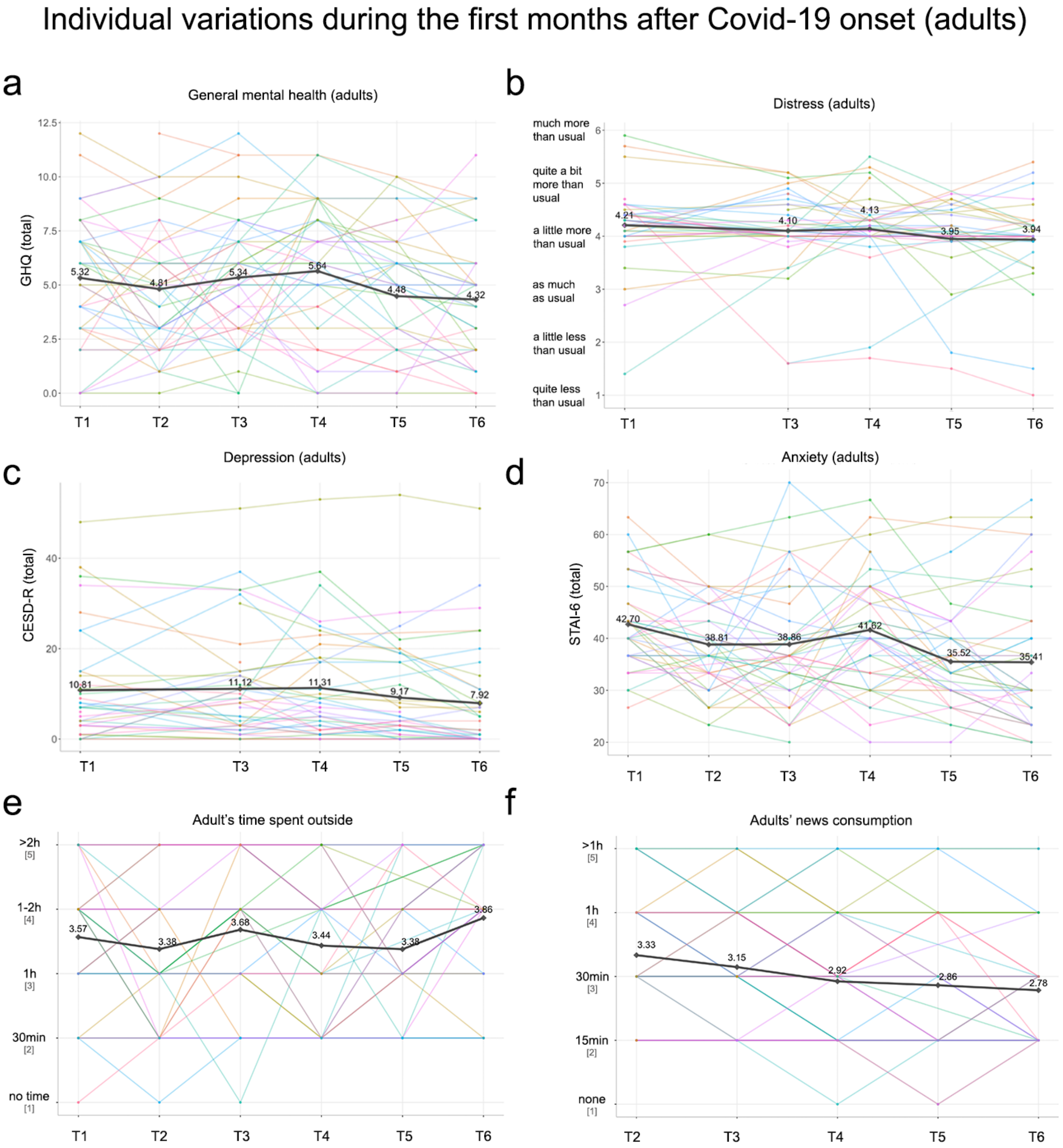

Figure 2. Variations of group (bold) and individual (colorful) scores in mental well-being across the first months after Covid-19 onset in adults. (**a**) Variation in scores of general mental health. (**b**) Variation in distress scores. (**c**) Variation in depression scores. (**d**) Variation in anxiety scores. (**e**) Variation in time spent outside. (**f**) Variation in news consumption.

Well-being during Covid-19 in adults

32.56% of all adults reported increased depression scores indicating the presence of subthreshold depressive symptoms ($CESD_{total} \geq 16$) with 4.65% meeting the criteria for a major depressive episode at least once. The prevalence of clinically significant anxiety was 34.88%. Group average scores reached clinically significant levels of anxiety at T1 (mean = 42.70, SD = 8.952) and T4 (mean = 41.62, SD = 8.798). Group average scores of subjective burden were in the moderate range (BSFC-s scores of 5–14[39]) throughout the whole assessment period (**Fig. 3**).

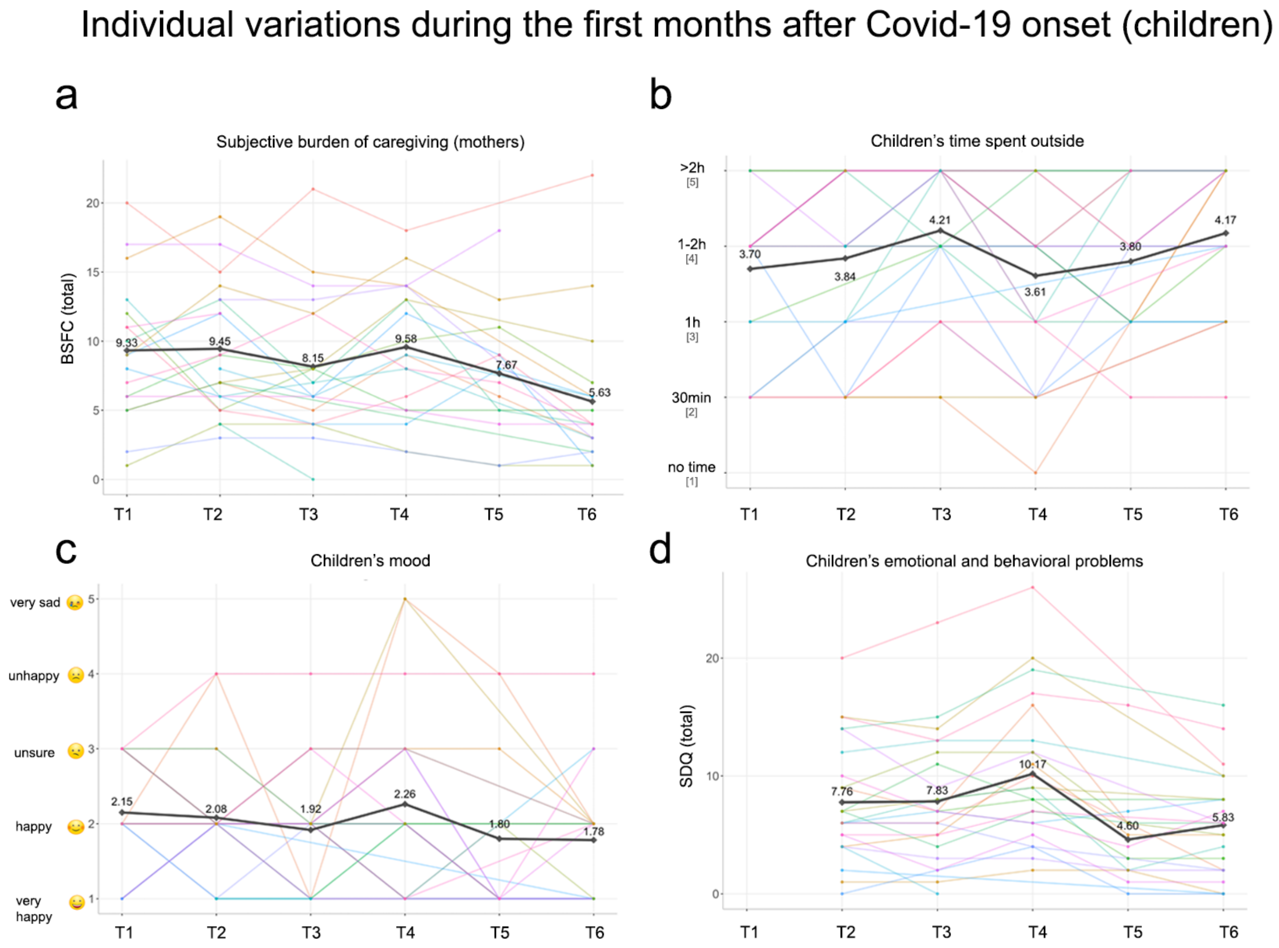

Figure 3. Variations of group (bold) and individual (colorful) scores in mental well-being across the first months of Covid-19 onset in children and mothers. (**a**) Variation in mother's subjective burden. (**b**) Variation in children's time spent outside. (**c**) Variation in children's mood. (**d**) Variation in children's emotional and behavioral problems.

When estimating the effect of restrictions on mental health longitudinally, linear mixed-effect models revealed a small but significant decrease in depression ($\beta = -0.04$), anxiety ($\beta = -0.61$), and burden of caregiving ($\beta = -0.26$) scores with each week passing by. There was a non-significant decrease in general health ($\beta = -0.06$) and distress ($\beta = -0.02$) scores. A detailed summary of all models is included in Table 2.

For the categorical variables Friedman test of differences revealed significant variations in *time spent outside* ($\chi^2 = 18.422$, $p = 0.002$) and *news consumption* ($\chi^2 = 25.177$, $p < 0.001$). Follow-up Bonferroni-corrected pairwise comparisons showed no significant differences for time spent outside between timepoints. For news consumption, follow-up pairwise comparisons showed significant differences between timepoints T2 and T6 (Fig. 2).

Well-being during Covid-19 in children

Linear mixed-effects models indicated a significant decrease in children's scores of conduct problems ($\beta = -0.04$), hyperactivity ($\beta = -0.03$), peer problems ($\beta = -0.03$) and overall emotional and behavioral problems ($\beta = -0.04$; total score of SDQ), whereas there was a non-significant decrease in emotional problems ($\beta = -0.003$) and increase in prosocial behavior ($\beta = 0.08$). A detailed summary of all models is included in Table 3. Friedman test revealed a significant variation in *time spent outside* ($\chi^2 = 21.002$, $p < 0.001$), with significant differences between timepoints T1 and T3. A significant variation over time was also revealed in *mood* ratings ($\chi^2 = 13.425$, $p = 0.020$), however, post-hoc pairwise comparisons remained non-significant. One-way analysis of variance indicated no significant difference in behavioral and emotional problems in children when comparing pre-Covid-19 scores with average scores obtained during Covid-19 (Supplementary Table S2).

Table 2. Linear mixed models in adults estimating the effect of time after Covid-19 onset on mental health indices.

	CESD (log)			**STAI**			**BSFC**			**GHQ**			**Distress**		
Predictors	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*
Intercept	2.05 (0.17)	1.72 – 2.37		42.58 (1.41)	39.82 – 45.33		10.07 (0.97)	8.16 – 11.98		5.49 (0.43)	4.65 – 6.34		4.22 (0.12)	3.99 – 4.46	
Duration (weeks)	-0.04 (0.02)	-0.07 – -0.01	**0.012**	-0.61 (0.16)	-0.93 – -0.29	**0.001**	-0.26 (0.08)	-0.42 – -0.09	**0.003**	-0.06 (0.04)	-0.13 – 0.02	0.162	-0.02 (0.02)	-0.05 – 0.01	0.218
ICC	0.78			0.59			0.56			0.59			0.67		
N	215/43			258/43			132/22			258/43			215/43		

CESD = Center of Epidemiologic Studies Depression Scales, STAI = State and trait anxiety inventory (state anxiety sum scores), BSFC-s = Burden scale for family caregivers (mean score), GHQ = General health questionnaire (mean score), Distress = modified Kessler Psychological Distress Scale (mean), SE = standard error, CI = confidence interval, Duration (weeks) = fixed effect, weeks passed since restrictions have been introduced, ICC = intraclass correlation coefficient, N = (number of observations)/(number of participants), p-values have been estimated using Satterthwaite approximation, **significant effects in bold**.

Table 3. Linear mixed models estimating the effect of time after Covid-19 onset on children's behavioral and emotion problems.

	Conduct problems (log)			**Emotional problems (log)**			**Hyperactivity (log)**			**Peer problems (log)**			**Prosocial behavior**			**Total (log)**		
Predictors	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*	*Estimates (SE)*	*CI (95%)*	*p*
Intercept	1.02 (0.15)	0.73 – 1.32		0.55 (0.17)	0.23 – 0.88		1.38 (0.14)	1.10 – 1.67		1.04 (0.14)	0.77 – 1.31		5.96 (0.46)	5.06 – 6.86		2.20 (0.15)	1.91 – 2.49	
Duration (weeks)	-0.04 (0.01)	-0.07 – -0.01	**0.012**	-0.003 (0.02)	-0.03 – 0.03	0.834	-0.03 (0.01)	-0.05 – -0.00	**0.047**	-0.03 (0.01)	-0.06 – -0.01	**0.016**	0.08 (0.05)	-0.00 – 0.17	0.075	-0.04 (0.01)	-0.07 – -0.02	**0.001**
ICC	0.77			0.49			0.72			0.56			0.58			0.66		
N	130/26			130/26			130/26			130/26			130/26			130/26		

SE = standard error, CI = confidence interval, Duration (weeks) = fixed effect, weeks passed since restrictions have been introduced, ICC = intraclass correlation coefficient, N = (number of observations)/(number of participants), p-values have been estimated using Satterthwaite approximation, **significant effects in bold**.

Mother-child associations

The multiple regression analyses including age and sex of the children revealed that the full model for mothers' subjective burden of caregiving explained 52.7% (ß=0.763, $t(22)=4.762$, $p<0.001$) of the variance in children's emotional and behavioral problems (complete model: $F(3,22)=8.173$, $p<0.001$; $R^2=0.527$ [adjusted $R^2=0.463$]). Anxiety and depression in mothers did not enter the model. Children's self-reported mood was best predicted by mothers' depression scores (ß=0.660, $t(22)=4.136$, $p<0.001$). Depression scores explained 45.2% of variance in children's mood (complete model including depression, age and sex: $F(3,22)=6.037$, $p=0.004$; $R^2=0.452$ [adjusted $R^2=0.377$]). Mothers' experienced burden of caregiving and anxiety did not enter the final model.

Post-hoc follow-up assessments

Post-hoc multiple regression analyses revealed no impact of sex, news consumption, time spent outside or parenthood on variations in scores of anxiety, depression or distress in adults, as neither entered into the prediction model. For children, meeting friends (yes/no) explained 35.5% of the variation and entered into the model as a significant predictor of mood (ß=-0.601, $t(22)=-3.551$, $p=0.002$). Mood was negatively coded (lowest score representing the best mood and highest scores representing lowest mood/sadness), indicating that meeting friends was positively linked to a better mood. The model including meeting friends controlling for age and sex was established as a significant predictor of mood with an $R^2=0.380$ (adjusted $R^2=0.294$; $F(3, 22)=4.499$, $p=0.013$).

Children's qualitative reports

An overview about children's subjective statements is given in Fig. 4.

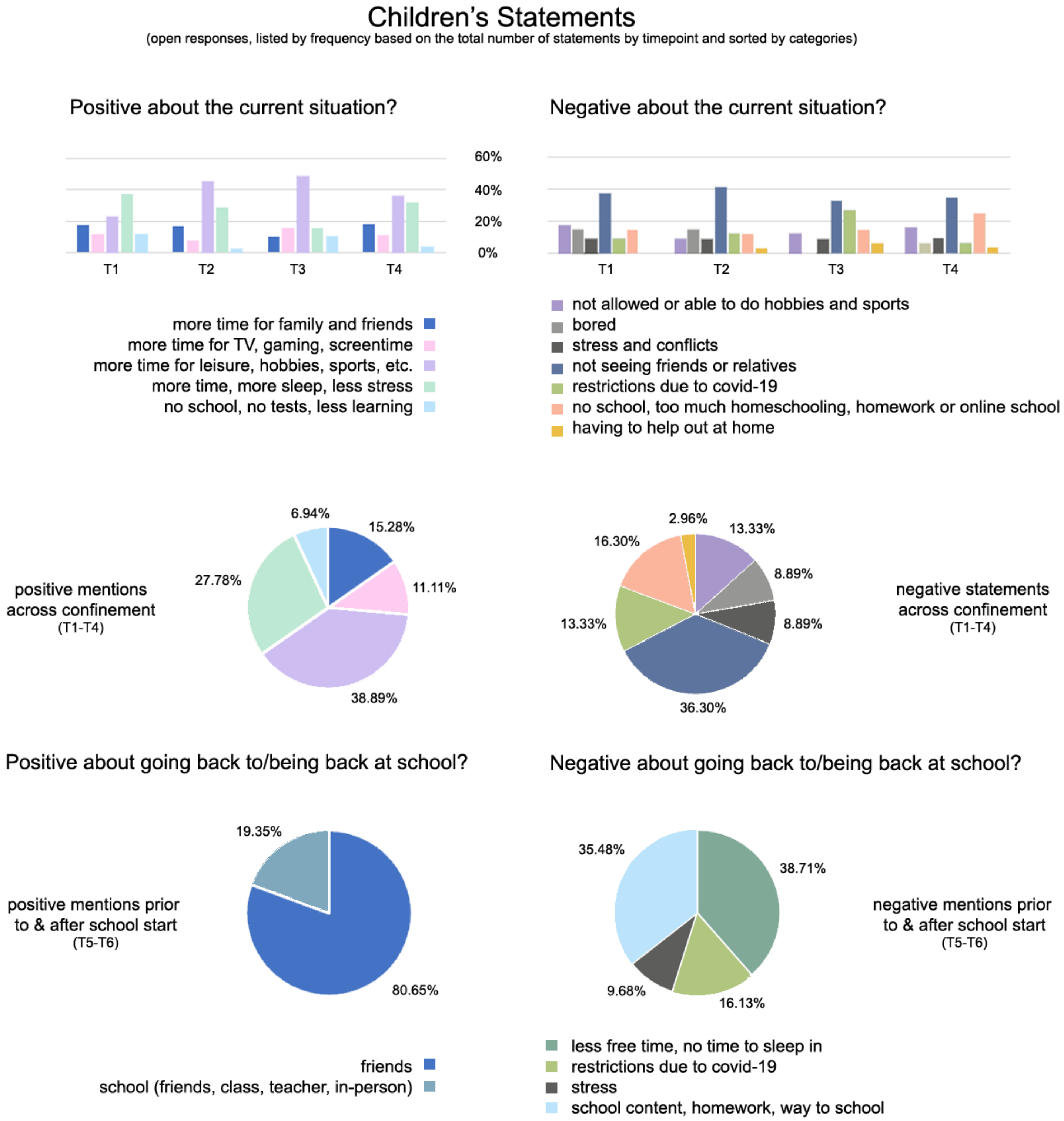

Figure 4. Qualitative measures of positive and negative associations with school closure or opening in children.

Neuroimaging findings

Across all participants, the neural correlates of mentalizing corresponded to brain regions previously associated with Theory of Mind[24], including bilateral temporoparietal and prefrontal regions or precuneus (see peak activation reports and figure in Supplementary Table S3, Supplementary Figure S2). The multiple regression analysis revealed that activation assessed prior to Covid-19 during mentalizing in right dorsolateral prefrontal cortex was a predictor of later development of fear about illness or contamination (ß=0.334, $t(60)=2.661$, $p=0.010$) constituting a significant model where dlPFC activation explained 13.9% of the variance in later reports of fear about illness or contamination ($R^2=0.139$; adjusted $R^2=0.096$; $F(3,60)=3.221$, $p=0.029$; including the covariates age and sex). Right temporoparietal junction did not enter the model as a significant predictor. When assessing the relationship between mentalizing-related activation and subjective burden, the right temporoparietal junction emerged as a significant predictor of burden (ß=0.623, $t(18)=3.276$, $p=0.004$), while the dorsolateral cortex did not enter into the model. The complete model explained 41.9% of the variation in subjective burden ($R^2=0.419$; adjusted $R^2=0.355$; $F(2,18)=6.493$, $p=0.008$; including age as a covariate; Fig. 5).

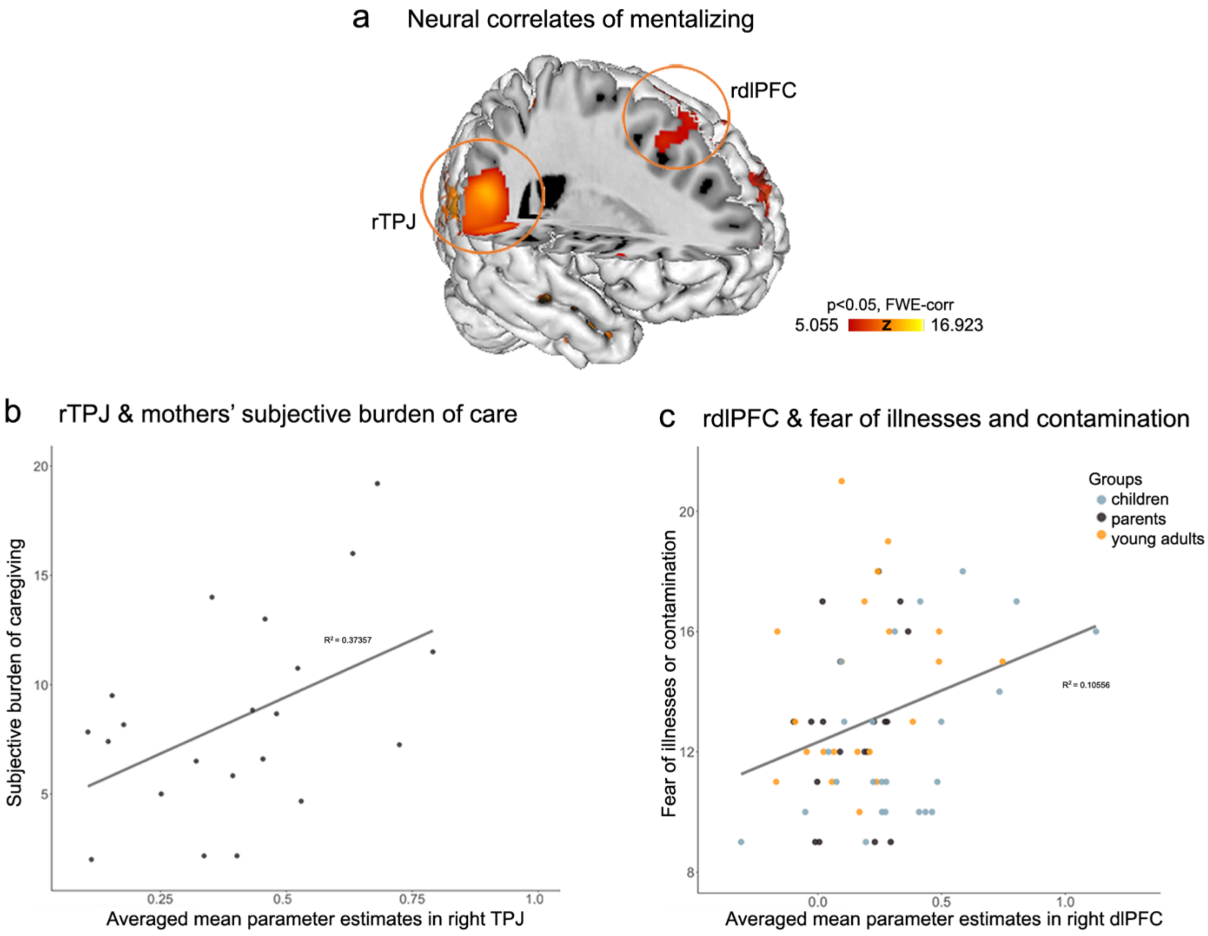

Figure 5. Functional brain correlates of mentalizing as assessed prior to Covid-19 onset and their associations with subjective burden and fear of illnesses and contamination reported during the early months of Covid-19. (a) Brain rendering for the neural correlates of mentalizing (Theory of Mind > control) across all participants (corrected for age and sex and whole brain FWE-corrected; regions of interest in right TPJ and dlPFC are circled in red). (b) Association between mean parameter scores during mentalizing in right TPJ and subjective burden of caregiving in mothers and (c) association of mean parameter scores in right dlPFC and fear of illnesses and contamination across all participants.

Discussion

We describe data on a small, but extensively characterized group of children and adults (N = 69, 41♀, age range = 7–51 years, including 26 children and their mothers), with reports across eight waves of testing, including seven assessment timepoints during the early months after Covid-19 onset in Switzerland and one assessment prior to the pandemic onset. Our findings report on mental well-being and psychosocial functioning in children and adults. The prevalence of clinically significant anxiety was 34.88%, and a 32.56% prevalence of subthreshold depression symptoms was observed across the 11 weeks. Caregiver burden was in the moderate ranges. Overall, scores of depression, anxiety and caregiver burden decreased over the course of the 11 weeks investigated. In children pre-pandemic levels of emotional and behavioral problems did not differ significantly from the average of the 11-week period during restrictions. Scores of conduct problem, hyperactivity, peer problems and overall emotional and behavioral problems in children decreased across time after Covid-19 onset. Well-being in mothers predicted mood and emotional and behavioral problems in children. In children meeting friends was a significant predictor of mood during restrictions. Additionally, neural correlates of mentalizing in prefrontal, but not temporoparietal regions, preceded the development of fear about contamination and illness across all participants. In mothers, higher neural activation in temporoparietal, but not frontal, regions during mentalizing preceded higher reports of subjective burden of care during restrictions. This may indicate that higher tendency to mentalize, usually considered beneficial for social interactions[49] and favorable when present in mother–child dyads[50], can be negatively associated with socioemotional functioning during prolonged stress.

Child behavior as measured by the SDQ or CBCL showed no difference when comparing pre-pandemic scores to those during restrictions, which is in line with longitudinal reports[7] observing a relatively stable level of problem behaviors after Covid-19 onset. Based on parental reports conduct problems, hyperactivity, peer problems and the overall level of emotional and behavioral problems decreased across time in the child group studied here. Emotional problems and prosocial behavior showed no significant changes during the 11-weeks assessment period. Additionally, children's time spent outside, and mood varied significantly. Variations in mood scores may be explained by several public holidays (Easter) around mid-restrictions. It may be possible that time spent outside during vacation allowed the meeting of friends, which was a relevant variable for increases in mood in children. Prior evidence highlights that prolonged school closure or restrictive measures are detrimental to children's physical and mental health and can have long-lasting consequences[14]. Conversely, the present study did not identify significant changes for emotional and behavioral problems of the children comparing pre- and post-pandemic onset levels. Our findings further indicate that meeting friends predicted better mood, which is in line with prior evidence emphasizing the importance of friendships and peer relationships in developmental groups[11,45].

Quantitative measures obtained were further supported by qualitative reports, which provide a unique insight into children's values and further highlight sources of resilience. More specifically, children mentioned more time for leisure, sleep, family, and friends or less stress or exams as positive attributes of school closure. Negative mentions centered around restrictions affecting social contacts, prohibiting hobbies or sports, or increased stress and conflict. Interestingly, across two time points, positive mentions about returning to schools across all children solely focused on social domains (e.g., meeting friends, class, teachers again or in-person schooling), whereas negative mentions included less sleep, less free time or increased stress and homework, or restrictions. Themes reported were in line with findings of qualitative reports during Covid-19[11,45].

Anxiety, depression and caregiver burden was high amongst adults with scores decreasing across the 11-week assessment period. Clinically significant levels of anxiety were reached at the beginning and after 7 weeks of restrictions. Furthermore, the 11-week prevalence of anxiety was 34.88%. An increase in anxiety due to Covid-19 and related restrictions has been reported previously[2,5,8,51], however, missing pre-pandemic scores hindered a direct investigation in the present group. Mixed-effects models reflected a decrease of anxiety scores across the first months after Covid-19 onset, which is in line with similar longitudinal studies indicating a decrease following a significant early impact in affect[2,51]. Similarly, a decrease in depressive symptomatology was observed. While group average scores of depression were in the normal range, it is notable that 32.56% of all adults reported heightened depressive symptoms and 4.65% qualified for a major depressive episode at least once. These observations mirror reports of heightened depression scores in the general population during Covid-19 (e.g., retrospective reports[2] or longitudinal data[6]). Mothers reported elevated levels of subjective burden of care (in the moderate range), which is in line with similar studies investigating parental burden during Covid-19[52]. Notably, a moderate burden of care has been associated with elevated risk for physical, psychosomatic, or mental health problems[39,52], indicating the need for parental programs mitigating possible stress-related health consequences. The experienced subjective burden of care decreased across the early months of investigation. Distress and general health, however, did not significantly change. Longitudinal studies to date have either reported a decrease or stagnation of depression or anxiety levels for the early months following Covid-19 onset across different countries[2,29,53]. Loosen et al.[29] for example suggest that such decreases in stress-related symptoms can partly be explained by adaptation, a phenomenon well-described in stress research[54]. Overall, first meta-analyses of studies compiling pre-/post mental health data report significant, but only small effects on anxiety and depression in adults[55]. Participant reports reflected significant changes in news consumption, reporting a higher amount of news consumed at the beginning and lower scores towards the end of the assessment period. Sex, news consumption, time spent outside or parenthood were not associated with variations in scores of anxiety, depression or distress in adults. This is somewhat surprising given prior evidence of the impact of each of these variables on mental well-being during Covid-19 (gender and parenting[44]; news consumption[2]; time spent outside[45]).

In the present study, mother–child variables were positively associated. Subjective burden of caregiving in mothers predicted emotional and behavioral problems in children, while anxiety and depression did not. This indicates that higher burden in mothers was linked to more problem behaviors in children. It is important to mention though that emotional and behavioral problems in the child were reported by the mother, thus reporting bias can't be excluded. We further investigated the effect of the mothers' well-being on children's self-reported mood, demonstrating that elevated depression in mothers was associated with children's mood ratings. Dyadic relationships are a primary vehicle for children's learning[9]. While commonly a driver of positive effects, it may also lead to negative consequences, as demonstrated in the example of vicarious conditioned fear learning in parent–child dyads[56]. We thus hypothesize, that negative mental health in adults may negatively impact children's well-being, possibly through learnt maladaptive coping or contagion. Increased parental stress and anxiety may lead to parental burnout[13] or increased aggression[15]. Intergenerational care during early years lays the foundation for healthy social skill development[57] and systemic mental health intervention programs commonly draw from this relationship[58]. Our data point towards a support of programs investing in increased parental support, which are expected to influence children's well-being positively.

The neural correlates of mentalizing as measured prior to the pandemic in prefrontal, but not temporoparietal brain regions, preceded the development of fear about contamination and illness in all participants. In mothers, higher neural activation during mentalizing in temporoparietal, but not frontal regions was associated with higher burden of caregiving during restrictions. Activation increases in the right temporoparietal junction are commonly reported as a response to tasks of mentalizing, as this area selectively responds to observed social interactions[59] and is part of the so-called paternal caregiver brain network[60]. Prefrontal areas are similarly engaged during tasks of mentalizing and are crucial for cognitive control processes[10]. Our data indicate that neural activation during mentalization in prefrontal cortex prior to Covid-19 may precede the development of fear of contamination and illnesses in both children and adults. The assessment of fear about contamination and illness required participants to make statements relating to the likelihood of oneself, a parent, a pet, or someone else in the world becoming sick and/or dying because of a virus or illness. Activation increases in prefrontal cortex have been linked to psychological state attributions, independent of whether they affect oneself, a relative, imagined people or animals[61] or cognitive control (i.e., emotion regulation). A higher tendency to think about other people's well-being, as reflected by higher mentalization-related activation in the prefrontal cortex, may thus be linked to the likelihood of developing fear about contamination and illness affecting ourselves and others.

Overall, better mentalizing has been associated with higher social competence, psychological and physiological functioning[22], while impairments have been associated with stress and depression[23]. Increased mentalizing skills in caregivers are beneficial for child development. For example, parental mentalization has been positively associated with regulatory skills in children[62,63], which may be protective during stressful life events[43]. However, the opposite effect may occur during stressful situations[17]. Higher levels of empathy in parents have for example been linked to better psychological and physiological health of their children, but also higher levels of inflammatory markers in the parents[63]. Moreover, higher levels of mentalizing abilities were shown to be associated with higher cortisol and heart rate reactivity in stressful situations[64]. This may temporarily be beneficial but may have a long-term negative impact depending on the intensity and duration of negative events. Our data indicate that mentalization can be negatively associated with increased burden and fear development in prolonged stressful situations.

In the present example, extensive phenotyping within individuals allow a comprehensive view and an opportunity to assess effects of time within individuals. Although the presented findings mostly align with Covid-19 literature they should be considered with caution due to the relatively small group size and less comprehensive pre-pandemic health measures. Research on the existence of potential subgroups will have to be further examined using larger and more diverse populations. An indication for possible subgroups reacting differently to stressful life events as associated with pandemics include reports of children that may in fact benefit or even thrive during restrictions[7]. A more detailed understanding of subgroups of individuals that are differently affected may increase opportunities to select the best fitting individualized treatments or prevention. Assessing direct subjective experience of the severity of impact by Covid-19 and associated restrictions would have been a valuable addition. Moreover, as the pre-pandemic assessment did not include comparable measures of mental health in the adult group, it is difficult to disentangle the effect of Covid-19 and related restrictions from pre-existing mental health symptoms. It remains to be investigated how far-reaching the herein observed negative effects on well-being are. Past work has indicated that early adversities can have an impact for life, with effects potentially being most significant in younger age and depending on the intensity of the experience[65]. An increased understanding of protective and/or risk factors and mechanisms leading to the development of stress-related psychopathologies may ultimately hold the potential to facilitate more personalized prevention and treatment strategies.

Data Availability

Behavioral mean scores are included in the manuscript and neuroimaging data is provided through NeuroVault (https://identifiers.org/neurovault.collection:9780). Further information or data may be obtained from the corresponding author.

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Contributions

N.M.R conceived the experiments. N.M.R., L.V.F., P.D. and R.B. designed, implemented, and conducted the experiments. R.B., A.N., J.A., L.V.F., and N.M.R. analyzed the results. N.M.R, R.B. and C.B.S. wrote the manuscript and each author reviewed the manuscript. All authors have made an important scientific contribution to the manuscript.

Ethics declarations

Competing interests

The authors declare no competing interests.

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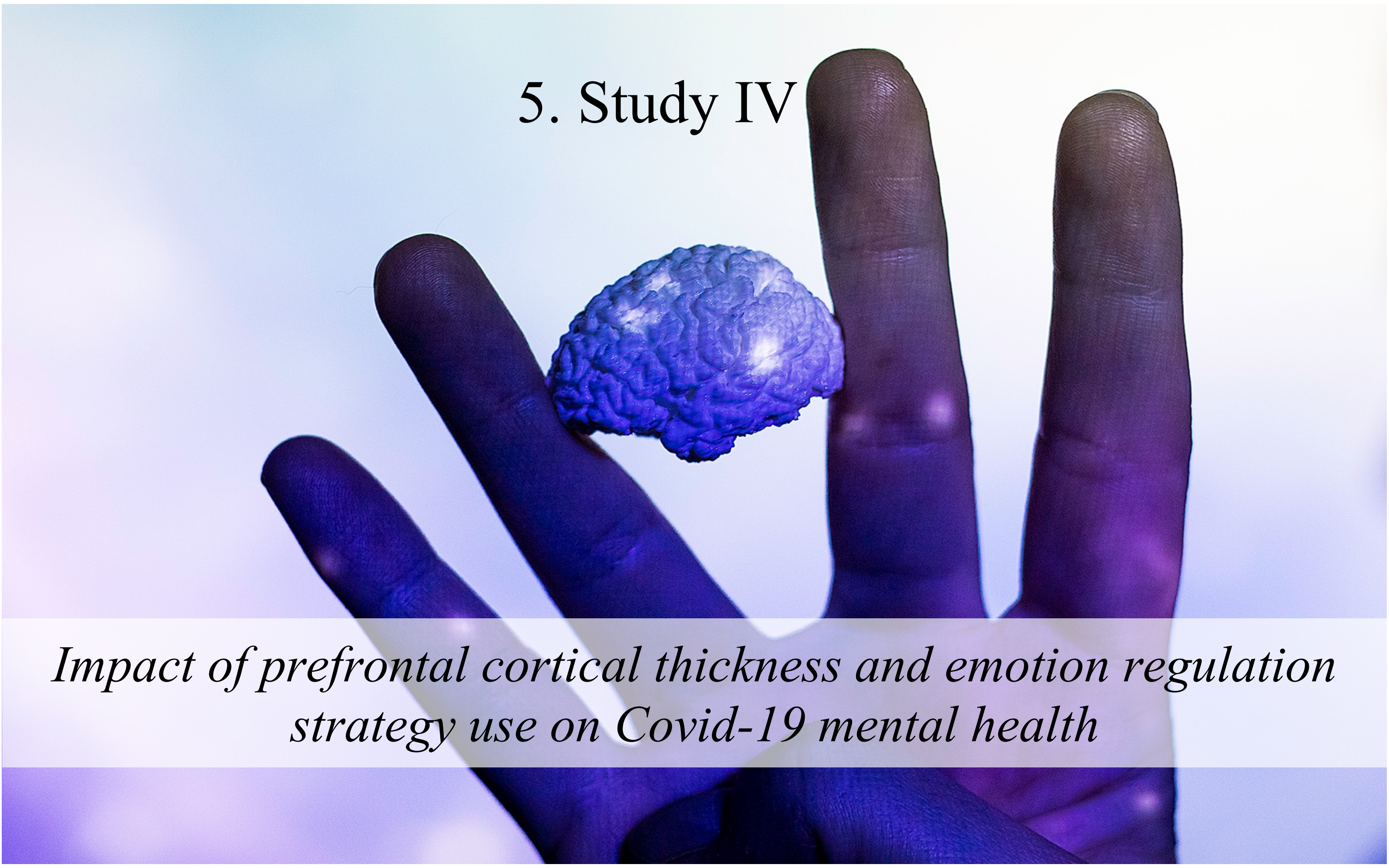

5. Study IV

Impact of prefrontal cortical thickness and emotion regulation strategy use on Covid-19 mental health

Plamina Dimanova[1,2]*, **Réka Borbás**[1,3]*, *Cilly Bernardette Schnider*[1], *Lynn Valérie Fehlbaum*[1,3], *Nora Maria Raschle*[1,2,3]

[1]*Jacobs Center for Productive Youth Development at the University of Zurich, Switzerland*

[2]*Neuroscience Center Zurich, University of Zurich and ETH Zurich, Switzerland*

[3]*University Psychiatric Clinic and University of Basel, Switzerland*

** both first authors contributed equally*

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Abstract

Background. Covid-19 and associated restrictions have been linked to negative mental health outcomes across the globe. Cognitive emotion regulation strategies, neurally supported by prefrontal and limbic regions, constitute means to mitigate negative affects resulting from adverse life experiences. **Methods.** Variations in cognitive emotion regulation strategy use, anxiety and depression were assessed in 43 adults (31♀/12♂, age=35.14±9.20y) during the first months following Covid-19 onset and at the end of 2020 (seven assessments). Direct and indirect effects of emotion regulatory brain structures assessed prior to the pandemic and emotion regulation strategy use during the pandemic were assessed in relation to mental well-being. **Results.** Varying levels of anxiety and depression were observed. While adaptive emotion regulation strategies were most frequently employed, maladaptive strategies explained the highest variation in anxiety and depression scores. The effectiveness of specific emotion regulation strategies varied. Momentary emotion regulation strategy use mediated the association between cortical thickness in right lateral prefrontal cortex assessed prior to the pandemic and mental health during the pandemic. Early mental health measures impacted later mental well-being. **Conclusion**. Maladaptive strategies have a negative effect on mental health during prolonged stress as induced by pandemics, providing possible targets for intervention.

Introduction

Emotion regulation skills describe a set of abilities allowing control over the intensity, duration or extent of an emotional experience (Gross, 2002; Ochsner et al., 2012). Proficient emotion regulation skills have been linked to healthy social, physical and psychological functioning, including one's own and others' physical and mental well-being (Tugade and Fredrickson, 2007). Reduced emotion regulation skills, however, have been linked to pathologies of childhood, adolescence or adulthood, including disruptive behavior disorders, depression or anxiety (Raschle et al., 2019; Megreya et al., 2020; Riaz et al., 2021). Healthy social functioning therefore relies on the interplay between mechanisms of emotion processing and cognitive control. Pandemics such as the coronavirus disease 2019 pandemic (Covid-19, named according to the year in which the outbreak was first identified and as recommended by the WHO) can induce a significant amount of stress and negative affect (Lee et al., 2007; Shanahan et al., 2020; Veer et al., 2020). Prolonged negative feelings resulting from events that are a threat to oneself, one's social status, self-identity or physical well-being, increase the risk to develop physical or mental health problems (Cohen et al., 2019), highlighting the need for interventions that may mitigate such effects. An individual's strategy and ability for emotion regulation is considered an essential contributing factor for the etiology, maintenance and treatment of mental health disorders (Cisler *et al.*, 2010; Cisler and Olatunji, 2012; Joormann and Stanton, 2016).

To date, the onset of Covid-19 and associated restrictions have been related to reduced general health and increases in neuropsychiatric symptoms, particularly anxiety and depression (Ensel and Lin, 1991; Ozamiz-Etxebarria et al., 2020; Shanahan et al., 2020; Borbás et al., 2021). First longitudinal assessments indicate that stress-related negative symptoms remained elevated during the first year following its onset (de Quervain et al., 2020; de Quervain, 2020; Gubler et al., 2020; Barendse et al., 2021). Emotional distress tends to be highest in younger individuals, in individuals with chronic diseases or pre-existing health conditions, females, and individuals living alone or in socioeconomic adversity (Adams-Prassl et al., 2020; de Quervain et al., 2020; Kwong et al., 2020; Ozamiz-Etxebarria et al., 2020). Findings of increases in emotional distress are complemented by reports of the opposite pattern: groups of individuals with improved mental well-being, indicating the need to consider interindividual differences (de Quervain et al., 2020; Kuhn et al., 2020; Achterberg et al., 2021).

In line with evidence demonstrating that a proficient use of adaptive emotion regulation skills may act as a possible buffer during adversity (Gross and John, 2003; John and Gross, 2004; Martin and Dahlen, 2005; Hu et al., 2014; Zahniser and Conley, 2018; Li et al., 2020; Shanahan et al., 2020), emerging evidence likewise indicates that the use of maladaptive emotion regulation strategies during the Covid-19 pandemic results in negative effects (Brehl et al., 2021; Muñoz-Navarro et al., 2021). This is in line with the notion that adaptive emotion regulation strategies are generally associated with better mental health, while the opposite is true for maladaptive skills (Garnefski et al., 2001). Adaptive skills include acceptance (being able to admit something took place), positive reappraisal (assigning positive meaning to an experience), refocus on planning (considering further steps and planning), positive refocus (attention shift towards something pleasant) and putting into perspective (setting an experience into context, for example by comparing the event to other experiences and relativizing its impact). Maladaptive emotion regulation strategies include catastrophizing (sole focus on detrimental consequences), rumination (recurring thoughts about negative feelings), other-blame (blaming someone else) and self-blame (blaming oneself for the negative experience).

Prior research indicates that emotion regulation strategies are differently effective in the modulation of an emotional experience and the direction of their effect on mental health outcomes may vary in dependence of context-specific factors (Balzarotti et al., 2016). For example, putting into perspective and acceptance are most commonly associated with beneficial outcomes, however, some studies report the opposite effect (Schroevers et al., 2007; Balzarotti et al., 2016). Such context-dependent variations might result from the type and intensity of the emotion experienced, vary with demographic characteristics of the individuals studied, but also depend on levels of controllability or the duration of the challenging circumstances (Martin and Dahlen, 2005; Aldao and Nolen-Hoeksema, 2012; McRae, 2016; Kobylińska and Kusev, 2019). Overall, the ability to adapt strategy use depending on context is considered beneficial for one's mental health (Kobylińska and Kusev, 2019). However, research on the temporal stability in the use of specific emotion regulation strategies is scarce. A study conducted in healthy participants investigated rumination and positive reappraisal over a 20-week period of everyday life, revealing relatively stable use of both strategies (Everaert and Joormann, 2020). To better understand the contextual effects on the efficacy of individual strategies longitudinal studies are needed. Such repeated measures studies can add beyond the mere examination of large-scale cross-sectional designs (Klapwijk et al., 2020).

Research using structural and functional magnetic resonance imaging (MRI) indicates that emotion regulation skills are supported by brain regions associated with cognitive control (e.g., prefrontal regions) and emotion processing (e.g., limbic regions including the amygdala (Buhle *et al.*, 2014; Kohn *et al.*, 2014; Braunstein *et al.*, 2017)). Emotion regulation skill acquisition is paralleled by the maturation of corresponding brain regions and strengthened by the connectivity between these (Baum et al., 2020). The coordinated interplay of brain regions responsible for emotion processing and cognitive control thus allow use of emotion regulation. Structural or functional alterations in any part of this network can lead to behavioral dysfunctions as reported for anxiety (Geng et al., 2016), depression (Zhang et al., 2018) or conduct disorder (Raschle et al., 2019). Varying levels of gray matter volume or cortical thickness of prefrontal or limbic brain structures have been associated with emotion regulation skills or disruptions thereof (Kühn et al., 2011; Vijayakumar et al., 2014; Ferschmann et al., 2021). Furthermore, studies investigating functional and structural connectivity point towards the importance of effective communication between prefrontal and limbic brain structures (Salzman and Fusi, 2010).

The present study (**i**) first aims to investigate variations in the use of specific emotion regulation strategies and mental health (i.e., depression and anxiety levels) in adults as assessed during the first year of the Covid-19 pandemic in Switzerland. Secondly (**ii**), the association of specific emotion regulation strategies in relation to mental well-being during the first pandemic months or towards the end of 2020 (early and later effects) are examined. Thirdly (**iii**), structural brain correlates assessed before the pandemic associated with emotion regulation (i.e., lateral prefrontal cortex and amygdala (Phan et al., 2005; Raschle et al., 2019; Berboth and Morawetz, 2021)) are investigated. More specifically, the mediating role of emotion regulation strategy use on the association of emotion regulatory brain structures assessed before pandemic onset and later mental well-being (beginning or end of the first year following Covid-19 onset) is investigated. Based on prior evidence (de Quervain et al., 2020; de Quervain, 2020; Borbás et al., 2021) we expect that participants will report significant but varying, levels of anxiety and depression. We anticipate that adaptive emotion regulation strategies are employed more often than maladaptive ones (Gross and John, 2003; Cohen et al., 2019; Cruz et al., 2020). and that adaptive emotion regulation strategies may buffer, while maladaptive strategies may increase the risk of negative outcomes (Butler *et al.*, 2003; John and Gross, 2004; Martin and Dahlen, 2005; Hu et al., 2014). Furthermore, we test the hypothesis that the use of specific emotion regulation strategies may change across time (given scarce prior evidence a non-directional exploratory assessment of the link between specific strategy-use and psychological well-being is tested). Finally, we expect that emotion regulatory brain structures as assessed prior to Covid-19 support the use of specific emotion regulation strategies which mediate the association between emotion regulatory brain structure and mental well-being during the pandemic (with adaptive strategies having a positive and maladaptive strategies having a negative influence on mental health).

Materials and Methods

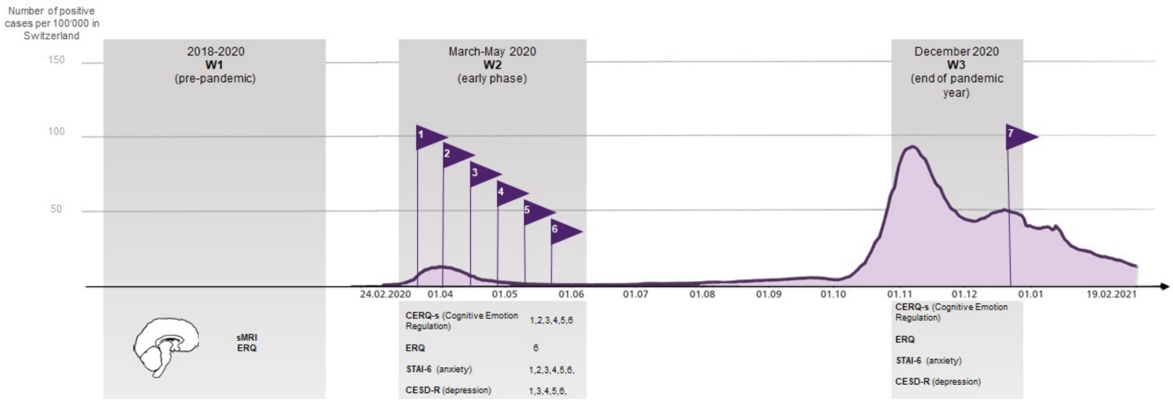

Figure 1. Study design. Data acquisition during the first year after Covid-19 onset in Switzerland followed initial baseline testing prior to pandemic onset (wave 1 (**W1**)). A second wave of assessments (wave 2 (**W2**)) included six biweekly testing spanning 11 weeks between March and May 2020 (**T1-T6**) and a third wave of assessments including one battery of questionnaires (**T7**; wave 3 (**W3**)) was completed at the end of the first pandemic year in December 2020. Testing relevant to the present study, targeting brain structure (assessed before Covid-19 onset), emotion regulation skills and strategy use and mental well-being (i.e., anxiety, depression), are listed here. *Notes*: sMRI: structural Magnetic Resonance Imaging, ERQ: Emotion Regulation Questionnaire, CERQ-s: Cognitive Emotion Regulation Questionnaire – short form, STAI-6: short form of the Strait-Trait Anxiety Inventory, CESD-R: Center for Epidemiologic Studies Depression Scale Revised; the violet line represents the daily incidence rate of individuals tested positive for Covid-19 per 100’000 in Switzerland.

Participants and design

Participants who had previously taken part in a cross-sectional neuroimaging study and agreed to being re-contacted were invited to participate (Borbás et al., 2021). Study design and assessments relevant to the present investigation are presented in **Figure 1**. Baseline (2018-2020; wave 1 (**W1**)) included behavioral testing and neuroimaging. All participants were of average intelligence or above (according to the International Standard Classification of Education ((ISCED; (Co-operation and Development, 1999)). Forty-three participants (31♀/12♂; average age=35.14±9.20y/range 22-51y;) agreed to participate in follow-up assessments. Retention rate per time point is reported in **Supplementary Table 2.1**.

All procedures were approved by the local ethics board (Ethikkomission Nordwest- und Zentralschweiz); participants signed an informed consent form.

Behavioral testing

The German short-form of the Cognitive Emotion Regulation Questionnaire (CERQ-s; (Garnefski and Kraaij, 2007)) was employed to assess state emotion regulation strategy use (six repeated assessments across W2: T1-T6, one testing at W3: T7). Mental well-being (W2-W3) was measured through the short-form of the State-Trait Anxiety Inventory (STAI-6; (Marteau and Bekker, 1992)) and by the Center for Epidemiologic Studies Depression Scale–Revised (CESD-R; German (Schmitt, 2016)). Trait emotion regulation skills were assessed once for each wave using the Emotion Regulation Questionnaire (ERQ; (Gross and John, 2003; Abler and Kessler, 2009)). The full assessment list is provided in **Supplementary Methods** and **Supplementary Table 2.2**).

Structural MRI

Structural T1-weighted MPRAGE data was acquired on a Siemens 3T-Prisma scanner (specifics in **Supplementary Methods**). Structural MRI data was preprocessed in FreeSurfer v7.1.0 (https://surfer.nmr.mgh.harvard.edu/) using the automated "recon-all" stream including motion correction, intensity-normalization, Talairach-registration, skull-stripping, removal of non-brain tissue, segmentation, tessellation, smoothing and cortical parcellation (Dale et al., 1999; Fischl et al., 1999). The quality of segmentation and reconstruction was visually inspected. Cortical thickness (CT) and gray matter volume (GMV), were reckoned on region-level as defined in the Desikan/Killiany atlas (Desikan et al., 2006). Amygdala was defined through the automatic segmentation, bilateral lateral prefrontal cortex (lPFC) regions of interest were derived based on average (for CT) or estimated total intracranial volume scaled sum (for GMV) of caudal middle frontal, rostral middle frontal regions, pars opercularis, pars triangularis, and pars orbitalis, in line with (Boes et al., 2012). We chose to investigate one key region of the emotion processing (i.e., amygdala) and one key region of the cognitive control network (i.e., lateral prefrontal cortex) respectively, since the intricate interplay between neural structures supporting emotion regulation and neural structures supporting affect processing have been suggested to best reflect the modal model of emotion regulation (Gross, 1998; Kohn et al., 2014) and since this influence has been commonly reported for both key structures (Kohn et al., 2014; Raschle et al., 2019; Berboth and Morawetz, 2021).

Data analysis

Analysis of the behavioral data was based on an imputed dataset, where missing values were replaced using predictive mean matching as implemented in the Multivariate Imputation by Chained Equations package in R (Buuren and Groothuis-Oudshoorn, 2010). Repeated measures acquired biweekly during W2 (between March and May 2020) were combined into one average W2-score. All analyses were conducted in IBM SPSSv27 (IBM corp, Armonk, NY, USA) and R (https://www.r- project.org/).

Early and late behavioral correlates during the first pandemic year. W2-W3 comparisons for anxiety, depression, and emotion regulation were conducted using one-way repeated measures analysis of covariance (ANCOVA; covariates: age and sex). The percentage of adults exceeding clinically relevant cut-off scores for anxiety (>40 for STAI-6 total; (Spielberger, 1983; Bekker et al., 2003)) and depression (>16 in CESD-R_{total}; https://cesd-r.com/cesdr/) is reported and number of people above clinically relevant thresholds at W2 and W3 were compared using chi-square tests.

Behavioral variations over time. To meet aim (i), variation in mental well-being and emotion regulation scores were examined by use of mixed-effect models and a bottom-up approach using the 'lme4' package in R (Bates et al., 2012) to test for linear and non-linear effects of time over the course of all seven repeated measurements collected. Subjects were entered as random effects accounting for non-independent data (i.e., same individuals participating at each time point), while weeks since the first assessment were entered as a fixed effect. The model allowed for random intercept (possible differences in scores at the start) and slope (since previous reports support individuals reacting differently to the pandemic). Using the Satterthwaite approximation (Luke, 2017) and the 'lmerTest' package (Kuznetsova et al., 2014) *p*-values were obtained. Due to right skewness for anxiety, depression, maladaptive strategies, catastrophizing, other-blame, positive reappraisal, refocus on planning, rumination, self-blame, putting into perspective and positive refocus, data was log-transformed. Furthermore, the frequency of adaptive and maladaptive CERQ-strategies employed at each assessment point was compared (paired sample t-tests for seven time points; significance level adjusted for multiple comparisons $p<0.007$).

Emotion regulation strategy use and mental well-being. To investigate aim (**ii**), testing the use of emotion regulation strategies in relation to variations in mental well-being, we employed multiple regression analyses. Anxiety or depression scores from the beginning (W2) and after ten months past Covid-19 onset (W3) were entered as the dependent variable and the nine emotion regulation strategies were entered as predictors, while controlling for participants' sex and age.

To evaluate the relationship between maladaptive/adaptive emotion regulation strategies and mental well-being (anxiety and depression) across 2020, four bivariate correlations were calculated. Maladaptive or adaptive emotion regulation strategies (two scores per person per assessment point) and anxiety and depression (two scores per person per assessment point) were correlated. Alpha-level significance was adjusted for multiple comparisons ($p<0.0125$).

Brain structure, emotion regulation, and mental well-being. To meet aim (**iii**), the association between structural brain markers assessed prior to Covid-19 pandemic (i.e., GMV and CT) in a priori defined emotion regulatory regions (bilateral lPFC and amygdala), emotion regulation strategies used, and mental health was assessed through mediation analyses while controlling for age, sex, months passed since individual MRI sessions and ISCED (a proxy to socioeconomic status and IQ (Feinkohl et al., 2021). To identify the variables of interest: (**1**) the emotion regulation strategy explaining the highest degree of variation in anxiety or depression for W2 and W3 was selected; (**2**) a priori defined structural brain measures explaining the highest degree of emotion regulation strategy use at W2 were selected. According to the hypothesized mediation framework (**Figure 2**) it is assumed that brain structure may be altered, as suggested by reports observing volumetric changes in healthy participants in anxiety and stress-related brain regions following Covid-19 onset (Salomon et al., 2021). Consequently, brain structures entering the model in relation to later outcome (W3) remained the same, but mental well-being at W2 was further added as a mediator allowing for the testing of an indirect effect.

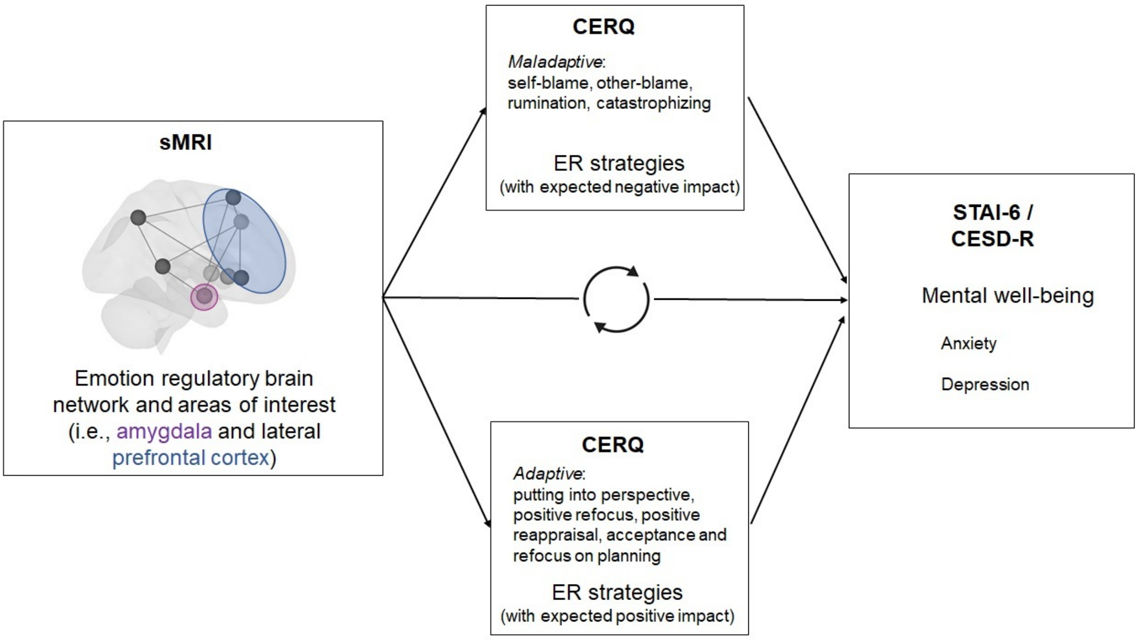

Figure 2. Overview of the hypothesized parallel multiple mediation model. We tested the hypothesis that emotion regulatory structural brain characteristics (i.e., in prefrontal cortex and

amygdala) assessed prior to Covid-19 onset enable the momentary use of adaptive and maladaptive cognitive emotion regulation strategies during the pandemic (Raschle et al., 2019; Berboth and Morawetz, 2021). Brain areas such as prefrontal cortex (in blue) and the amygdala (in purple) are key players within the emotion regulation networks for cognitive control and affect processing, respectively (Kohn et al., 2014). Positive (adaptive) or negative (maladaptive) strategies are expected to either positively or negatively mediate well-being as assessed by levels of anxiety or depression (Carver et al., 1999; Nowlan et al., 2015; McRae, 2016). The model acknowledges that prolonged use of maladaptive or adaptive emotion regulation strategies and long-term negative emotions may in turn impact brain structure (as indicated by circular arrows). *Notes:* sMRI: structural Magnetic Resonance Imaging, CERQ: Cognitive Emotion Regulation Questionnaire, STAI-6: short form of the Strait-Trait Anxiety Inventory, CESD-R: Center for Epidemiologic Studies Depression Scale Revised.

Mediation analyses were conducted using the PROCESS model 4 by Hayes (2017) to assess emotion regulation strategies as mediators of the relation between brain correlates (step 2) and W2-anxiety or -depression scores; covariates included age, sex, months passed since the neuroimaging session and ISCED. Double mediations were performed through PROCESS model 6 to test whether emotion regulation strategies used at W3 and/or psychological well-being at W2 mediated the association between brain structure and psychological well-being at W3. Bootstrapping was set to 10000 samples in each model.

Results

Early and late behavioral correlates during the first pandemic year

Table 1. Group characteristics and comparisons between the second (W2) and third (W3) assessment waves. * indicates significance at *p*<0.05

N=43; 31 females; mean age: 35.14 ± 9.20 y							
	W2	M ± SD		**W3**	M ± SD	*F*(1,40)	η2
Time since first testing	in months	18.76 ± 7.03	**Time since first testing**	in months	27.76 ± 7.03		
STAI-6	anxiety	38.85 ± 8.13	**STAI-6**	anxiety	41.32 ± 9.43	5.064*	0.020
CESD-R	depression	9.53 ± 10.40	**CESD-R**	depression	11.58 ± 12.15	2.765	0.009
ERQ	cognitive reappraisal	4.64 ± 1.02	**ERQ**	cognitive reappraisal	4.81 ± 0.96	1.684	0.008
	expressive suppression	3.46 ± 1.05		expressive suppression	3.11 ± 1.14	4.353*	0.034
CERQ-s	self-blame	2.40 ± 0.97	**CERQ-s**	self-blame	2.23 ± 0.57	2.585	0.011
	acceptance	7.07 ± 1.71		acceptance	6.98 ± 2.09	0.124	0.001

	rumination	3.71 ± 1.27		rumination	3.77 ± 1.34	0.189	0.001
	positive refocusing	5.24 ± 1.66		positive refocusing	5.30 ± 1.87	0.075	0.000
	refocus on planning	5.09 ± 1.23		refocus on planning	4.58 ± 1.62	3.507	0.033
	positive reappraisal	5.29 ± 1.66		positive reappraisal	5.14 ± 2.17	0.364	0.002
	putting into perspective	5.88 ± 1.85		putting into perspective	5.40 ± 2.01	2.438	0.016
	catastrophizing	2.70 ± 0.93		catastrophizing	2.58 ± 0.91	0.726	0.004
	other-blame	3.25 ± 1.21		other-blame	3.56 ± 1.44	2.230	0.014
CERQ-s	adaptive strategies	5.71 ± 1.08	**CERQ**	adaptive strategies	5.48 ± 1.27	2.191	0.010
Factors	maladaptive strategies	3.01 ± 0.80	**Factors**	maladaptive strategies	3.03 ± 0.71	0.056	0.000

W2/W3-group characteristics and differences are provided in **Table 1**. One-way repeated measures ANCOVA (W2-W3-comparison) indicated significant differences in anxiety and use of expressive suppression. On average 34.88% of all participants surpassed clinically relevant anxiety levels at W2, 48.84% at W3 (percentages not statistically different). Subthreshold clinically relevant levels of depression were reported by 20.93% at W2 and W3.

Behavioral variations over time

In **Figure 3, 4 and the Supplementary Figure 3.1** the individual variations (differently colored lines) and group average (black line) over seven assessments for mental well-being (anxiety and depression scores), the nine cognitive emotion regulation strategies, the adaptive and maladaptive strategies are depicted. Examining the effects of time revealed no significant variations for self-blame (β=-0.001), catastrophizing (β=-0.001), other-blame (β=0.002), positive refocus (β=0.0003) and cognitive reappraisal (β=0.001).

Changes in anxiety (β_{linear}=-0.02, $\beta_{quadratic}$=0.0005), adaptive strategies (β_{linear}=-0.05, $\beta_{quadratic}$=0.001), acceptance (β_{linear}=-0.08, $\beta_{quadratic}$=0.002), positive reappraisal (β_{linear}=-0.02, $\beta_{quadratic}$=0.0005), refocus on planning (β_{linear}=-0.03, $\beta_{quadratic}$=0.0004) and rumination (β_{linear}=-0.01, $\beta_{quadratic}$=0.0002) were best described by quadratic models indicating a continuous significant decrease from T1 to T6 followed by a significant increase in scores to T7. Putting into perspective was also best characterized by a quadratic model but the scores were increasing significantly from T1 to T6 and decreasing to T7 (β_{linear}=0.01, $\beta_{quadratic}$=-0.0003). The use of maladaptive strategies was significantly declining from T1 to T6 but no further change was observed to T7 (β_{linear}=-0.005, $\beta_{quadratic}$=0.0001).

Changes in depression scores were best described by a cubic model, with significant increase between T1 and T3 then decrease to T6, but increase anew to T7 (β_{linear}=0.12, $\beta_{quadratic}$=-0.02, β_{cubic}=0.0005; **Table 2**).

The employment of expressive suppression was significantly higher in the early (May 2020) compared to the late (December 2020) phase of assessments. However, when examining the trajectory of expressive suppression employment including all three time points (pre-pandemic, May 2020, December 2020; β=0.002) no significant change was indicated. This discrepancy stems from the different analytical approaches. More specifically, an ANCOVA is handling time as a categorical variable, while in the mixed-effects model time is regarded as a continuous variable, accounting for uneven spacing of data points. The results of both approaches should not be directly compared.

Paired *t*-tests comparing adaptive and maladaptive strategy use at each time point revealed significantly higher use of adaptive strategies at each timepoint (all $p<0.001$; details in **Supplementary Table 2.3**).

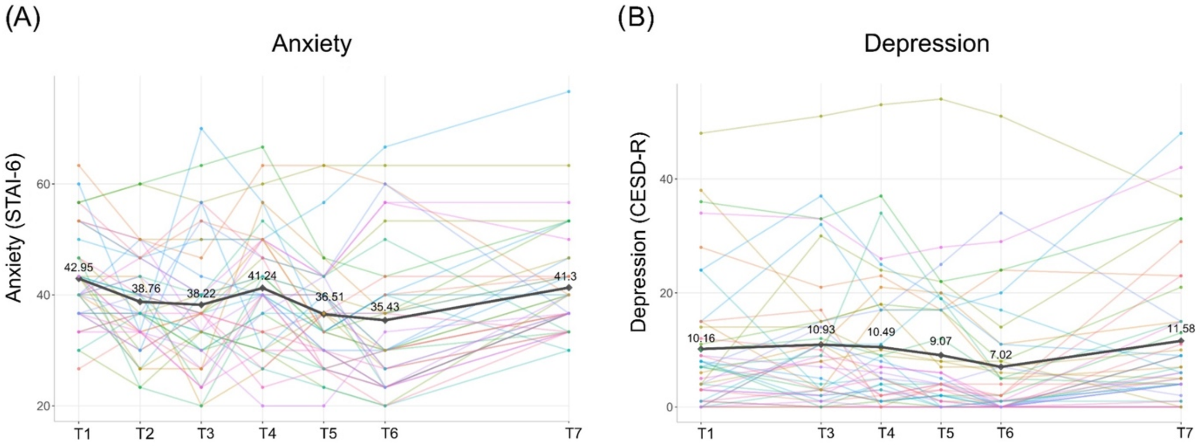

Figure 3. Variation of mental health scores over time. Inter-subject variations (different colors) and group average (black, bold) are displayed. (**A**) Anxiety levels over seven time points after Covid-19 onset and (**B**) depression levels over six time points. *Notes:* CESD-R: Center for Epidemiologic Studies Depression Scale Revised; STAI-6: short form of the Strait-Trait Anxiety Inventory.

Table 2. Mixed models estimating the effect of time on individuals' mental health. *Notes:* SE: standard error, CI: confidence interval, ICC: intraclass correlation coefficient; N: number of participants/ observations, *p*-values are estimated employing Satterthwaite approximation; significant effects are indicated in bold.

Variables		**Intercept**	**Duration (linear)**	**Duration (quadratic)**	**Duration (cubic)**	**ICC**	**N subjects/ observations**

Anxiety (log)	Estimate (SE)	3.74 (0.03)	-0.02 (0.004)	0.0005 (0.0001)		0.46	43/301
	CI (95%)	3.68 - 3.81	-0.03 – -0.01	0.0004 – 0.0008			
	p	**<0.001**	**<0.001**	**<0.001**			
Depression (log)	Estimate (SE)	1.87 (0.18)	0.12 (0.05)	-0.02 (0.01)	0.0005 (0.0001)	0.69	43/258
	CI (95%)	1.52 – 2.22	0.02 – 0.21	-0.03 – -0.01	0.0002 – 0.0007		
	p	**<0.001**	**0.017**	**<0.001**	**<0.001**		
Adaptive strategies	Estimate (SE)	5.93 (0.18)	-0.05 (0.02)	0.001 (0.0004)		0.69	43/301
	CI (95%)	5.58 – 6.28	-0.09 – -0.02	0.0003 – 0.002			
	p	**<0.001**	**0.003**	**0.010**			
Maladaptive strategies (log)	Estimate (SE)	1.39 (0.03)	-0.005 (0.003)	0.0001 (0.0001)		0.67	43/301
	CI (95%)	1.33 – 1.44	-0.01 – 0.001	-0.00001 – 0.0002			
	p	**<0.001**	**0.017**	0.079			
Cognitive reappraisal	Estimate (SE)	4.68 (0.13)	0.001 (0.001)				43/129
	CI (95%)	4.42 – 4.93	-0.002 – 0.004				
	p	**<0.001**	0.619				
Expressive suppression	Estimate (SE)	3.12 (0.16)	0.002 (0.001)			0.52	43/129
	CI (95%)	2.80 – 3.43	-0.001 – 0.004				
	p	**<0.001**	0.274				
Acceptance	Estimate (SE)	7.42 (0.30)	-0.08 (0.04)	0.002 (0.001)		0.52	43/301
	CI (95%)	6.48 – 8.00	-0.15 – -0.01	0.0002 – 0.004			
	p	**<0.001**	**0.020**	**0.028**			
Positive reappraisal	Estimate (SE)	1.88 (0.04)	-0.02 (0.004)	0.0005 (0.0001)		0.70	43/301
	CI (95%)	1.79 – 1.96	-0.03 – -0.01	0.0003 – 0.001			
	p	**<0.001**	**<0.001**	**<0.001**			
Positive refocus	Estimate (SE)	1.78 (0.04)	0.0003 (0.003)			0.68	43/301
	CI (95%)	1.69 – 1.87	-0.002 – 0.003				
	p	**<0.001**	0.809				
Refocus on planning	Estimate (SE)	1.86 (0.04)	-0.03 (0.004)	0.0004 (0.0001)		0.53	43/301
	CI (95%)	1.79 – 1.94	-0.03 – -0.01	0.0002 – 0.001			
	p	**<0.001**	**<0.001**	**<0.001**			
Putting into perspective	Estimate (SE)	1.83 (0.05)	0.01 (0.01)	-0.0003 (0.0001)		0.60	43/301
	CI (95%)	1.73 – 1.92	0.001 – 0.02	-0.001 – -0.0001			
	p	**<0.001**	**0.032**	**0.013**			
Rumination	Estimate (SE)	1.54 (0.04)	-0.01 (0.004)	0.0002 (0.001)		0.57	43/301
	CI (95%)	1.46 – 1.62	-0.02 – -0.001	0.00002 – 0.0005			
	p	**<0.001**	**0.039**	**0.030**			
Self-blame	Estimate (SE)	1.19 (0.03)	-0.001 (0.001)			0.62	43/301
	CI (95%)	1.14 – 1.25	-0.002– -0.0004				
	p	**<0.001**	0.171				
Other-blame	Estimate (SE)	1.38 (0.04)	0.002 (0.001)			0.54	43/301
	CI (95%)	1.30 – 1.46	-0.0001 – 0.004				
	p	**<0.001**	0.066				

Catastrophizing	Estimate (SE)	1.27 (0.03)	-0.001 (0.001)			0.54	43/301
	CI (95%)	1.21 – 1.34	-0.003 – 0.001				
	p	**<0.001**	0.388				

Emotion regulation strategy use and mental well-being

Multiple regression analyses revealed that anxiety and depression during W2 (March-May 2020) were significantly predicted by rumination and positive reappraisal (variation in anxiety explained: 61.2%; depression: 49.2%). Rumination explained 41.5% of variation in anxiety ($F(4,38)=15.001$, $p<0.001$; ß=0.730, $t(38)=6.953$, $p<0.001$), positive reappraisal explained 15.1% (negative association, ß=-0.396, $t(37)=-3.849$, $p=0.025$). The model for depression ($F(4,38)=9.194$, $p<0.001$) revealed a positive association of rumination (ß=0.702, $t(38)=5.837$, $p<0.001$; 40.6%) and negative association of positive reappraisal (ß=-0.275, $t(38)=-2.338$, $p=0.025$; 7.4%).

At W3 (December 2020), self-blame (ß=0.510, $t(39)=3.661$, $p<0.001$) explained 25.0% of the variance in anxiety ($F(3,39)=4.887$, $p<0.001$). The model for depression ($F(5,37)=12.118$, $p<0.001$) included three predictors, self-blame (ß=0.485, $t(37)=4.308$, $p<0.001$), rumination (ß=0.286, $t(37)=2.591$, $p=0.014$) and refocus on planning (ß=0.251, $t(37)=2.357$, $p=0.024$), explaining 38.3%, 8.3% and 5.7%.

Assessment of the relationship between adaptive or maladaptive strategy use and anxiety or depression revealed a significant link between higher use of maladaptive strategies and elevated levels of anxiety and depression. The use of adaptive strategies was negatively linked with anxiety (**Figure 5**), while the association between the use of adaptive strategies and depression was not significant.

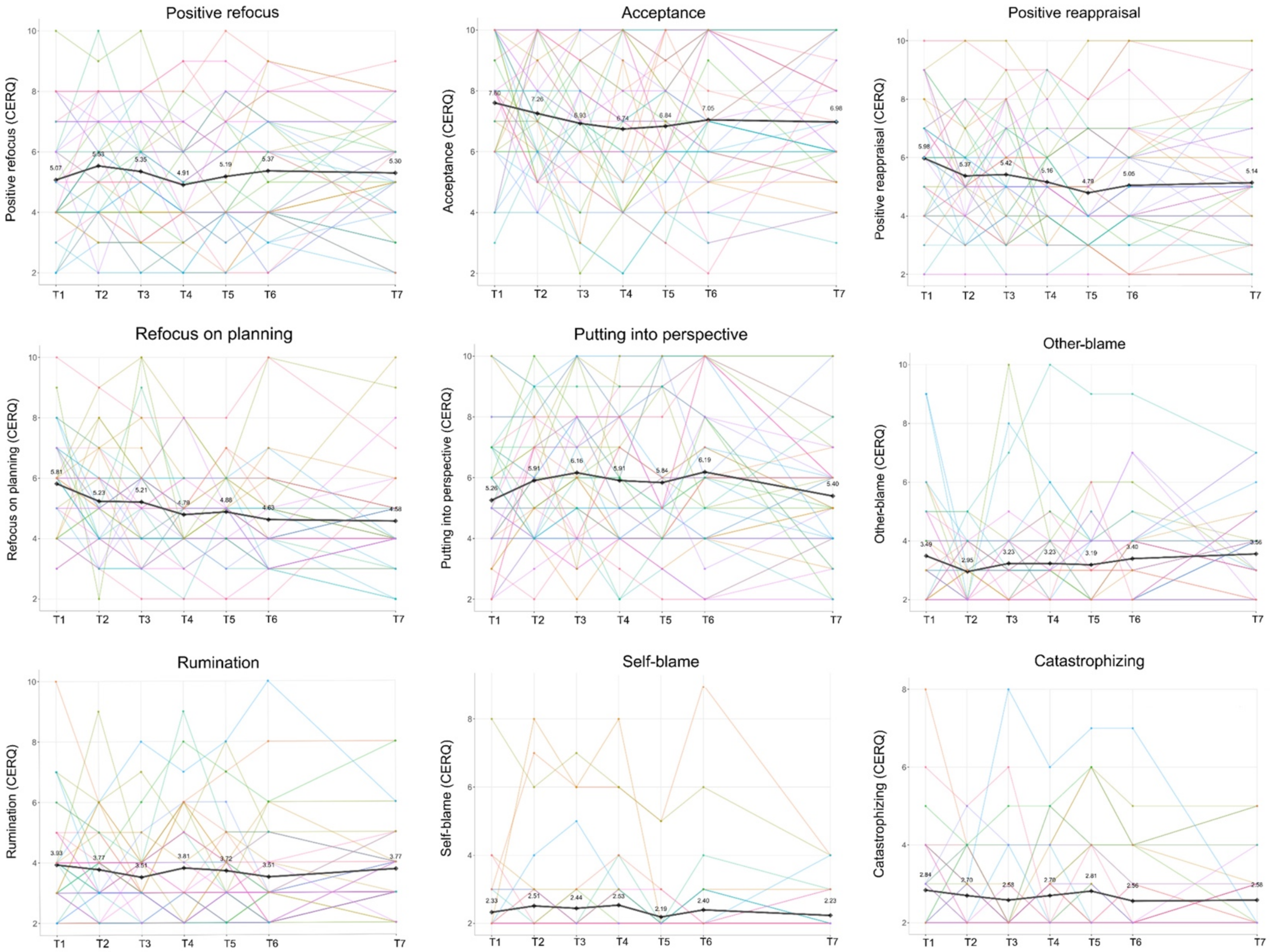

Figure 4. Variation in the use of nine cognitive emotion regulation strategies over seven time points following Covid-19 onset in Switzerland. Inter-individual variations (different colors) and the group average (bold black) are displayed. *Notes:* CERQ: Cognitive Emotion Regulation Questionnaire; the lowest employment of adaptive and maladaptive emotion regulation strategies is two, while the highest possible use is ten.

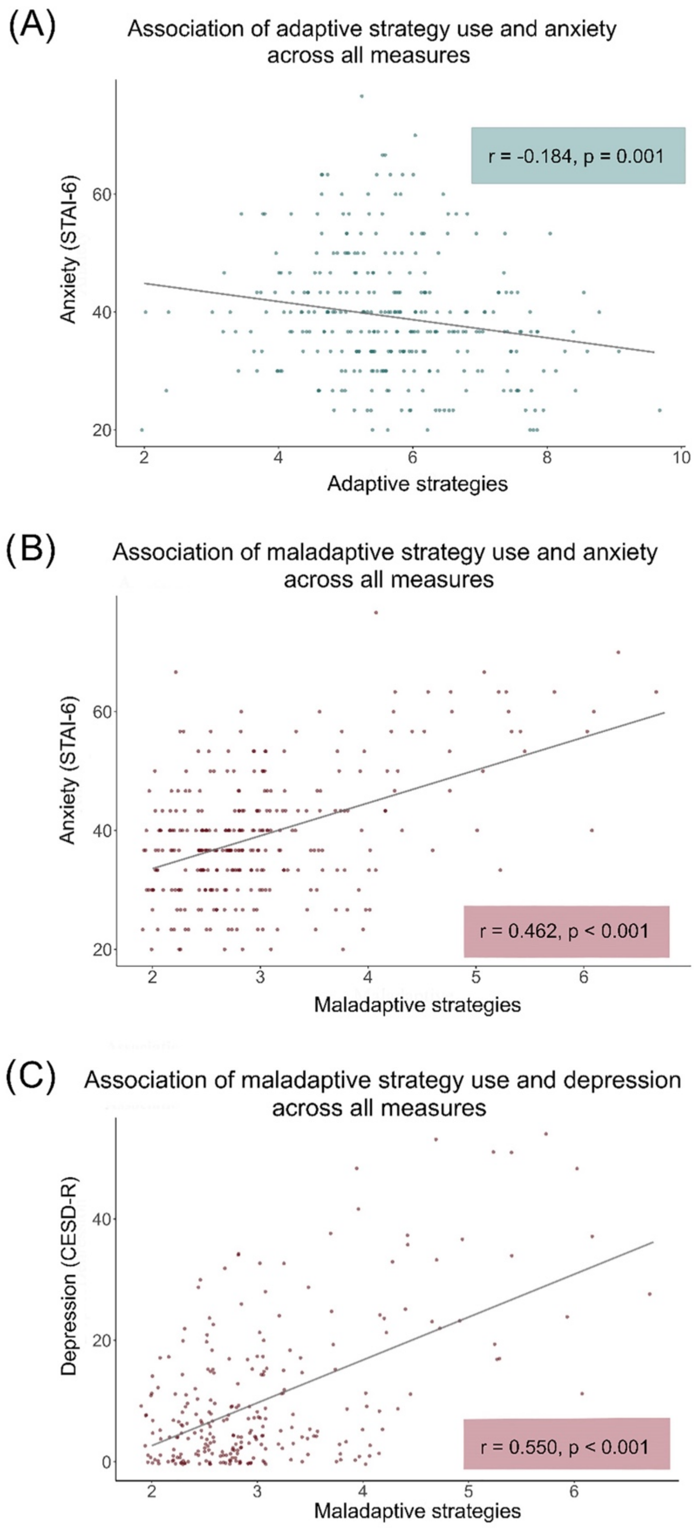

Figure 5. Association between adaptive (blue; **A**) or maladaptive (red; **B** and **C**) emotion regulation strategy use and mental well-being as represented by any answers given across the seven measurement time points by all individuals (total answer independent of person or testing point). Correlational displays indicate **(A)** a negative association between the use of adaptive strategies and anxiety levels; **(B)** a positive association between the use of maladaptive

strategies and anxiety levels and **(C)** positive relations between the use of maladaptive strategies and depression levels. *Notes:* CESD-R: Center for Epidemiologic Studies Depression Scale Revised, STAI-6: short form of the Strait-Trait Anxiety Inventory; the lowest employment of adaptive and maladaptive emotion regulation strategies is two, while the highest possible use is ten.

Brain structure and early emotion regulation strategy use and mental well-being

Two simple mediation models were built testing how emotion regulation strategy use at W2 mediated the association of emotion regulatory brain structure assessed before the pandemic and anxiety (model-1) or depression (model-2) at W2. In step 1 rumination was identified as the strategy explaining most variance at W2 in anxiety and depression through multiple regression analyses. Next (2) the association of a priori-defined emotion regulatory brain structures and rumination revealed that only cortical thickness in the right lateral prefrontal cortex (rlPFC$_{CT}$) remained a significant predictor of W2-rumination (β=0.540, $t(37)$=3.221, p=0.003), explaining 20.7% of the variance within the model ($F(5,37)$=2.628, p=0.039, R^2=0.262).

Model-1 included rlPFC$_{CT}$ as the predictor, W2-anxiety as the outcome, and W2-rumination as the mediator (**Figure 6(A)**). RlPFC$_{CT}$ was a significant positive predictor of W2-rumination (b=5.893, $t(37)$=3.221, p=0.003, R^2=0.262). W2-rumination was also a significant predictor of W2-anxiety (b=3.349, $t(36)$=3.958, p<0.001) and a significant mediator of the effect of rlPFC$_{CT}$ on W2-anxiety (b=19.735, *SE*=10.740, *95%CI* [3.407,44.950]). The direct effect of rlPFC$_{CT}$ was not significant (b=20.811, *SE*=10.655, *95%CI* [-0.798,42.420]), thus a full mediation was observed. The full model explained 53.72% of W2-anxiety score variations ($F(6,36)$=6.965, p<0.001, R^2=0.537).

Model-2 including depression as outcome (**Figure 6(B)**) revealed a significant positive prediction of rlPFC$_{CT}$ on W2-rumination (b=5.893, $t(37)$=3.221, p=0.003, R^2=0.262), however, it was not a direct predictor of W2-depression levels (b=23.004, *SE*=14.655, *95%CI* [-6.718,52.727]). Rumination was positively associated with depression (b=4.439, $t(36)$=3.814, p=0.001) via the indirect path and significantly mediated the effect of rlPFC$_{CT}$ on W2-depression (b=26.158, *SE*=15.227, *95%CI* [3.530,61.553]). The full model explained 46.43% of variance in W2-depression scores ($F(6,36)$=5.201, p=0.001, R^2=0.464).

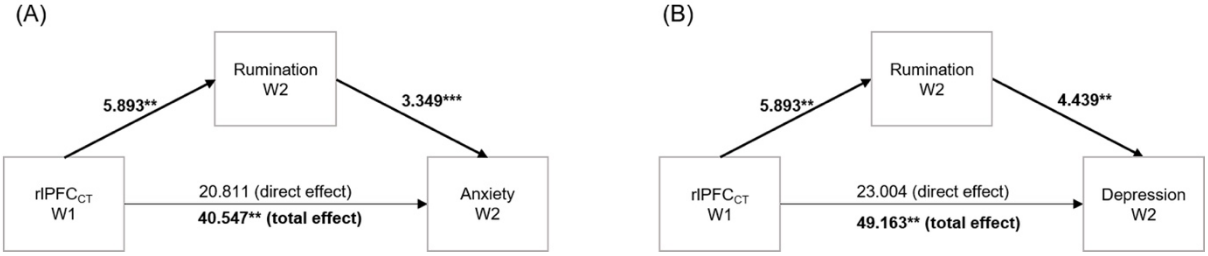

Figure 6. Mediation models investigating the relationship between rlPFC$_{CT}$ at W1 and mental well-being scores at W2. **(A)** Rumination at W2 mediates the relationship between rlPFC$_{CT}$ at W1 and anxiety scores at W2 (*b*=19.735, *SE*=10.740, *95%CI* [3.407,44.950]); (**B)** rumination at W2 mediates the association between rlPFC$_{CT}$ at W1 and depression levels at W2 (*b*=26.158, *SE*=15.226, *95% CI* [3.530,61.553]). Significant mediations are depicted as bold paths; *p<0.05, **p<0.01, ***p <0.001.

Brain structure and late emotion regulation strategy use and mental well-being

Self-blame was the emotion regulation strategy explaining the highest degree of variance in anxiety and depression at W3 (step 1). RlPFC$_{CT}$ was entered as a predictor. W3-anxiety or W3-depression were the outcome variables in the two models, while W2-anxiety or W2-depression were included as a first mediator, and W3-self-blame as a second mediator. Double mediation for W3-anxiety (**Figure 7(A)**) revealed that rlPFC$_{CT}$ was a significant positive predictor of W2-anxiety (*b*=40.547, *t*(37)=3.644, *p*=0.001, R^2=0.336), not for W3-self-blame (*b*=-0.088, *t*(36)=-0.060, *p*=0.952). W2-anxiety was a significant predictor for W3-self-blame (*b*=0.047, *t*(36)=4.610, *p*<0.001) and W3-anxiety (*b*=0.647, *t*(35)=3.192, *p*=0.003). W3-self-blame did not predict W3-anxiety (*b*=2.043, *t*(35)=0.785, *p*=0.438). Without consideration of mediators, the effect of rlPFC$_{CT}$ on W3-anxiety was significant (*b*=35.821, *t*(37)=2.654, *p*=0.012). This effect was reduced in the full model, rendering the direct effect non-significant (*b*=5.778, *t*(35)=0.456, *p*=0.651). W2-anxiety was a mediator in the relationship between rlPFC$_{CT}$ and W3-anxiety (*b*=26.215, *SE*=11.651, *95%CI* [8.400,54.076]). Mediations between rlPFC$_{CT}$ and W3-anxiety through W2-anxiety and W3-self-blame or through W3-self-blame only were not significant (*b*=3.927, *SE*=9.010, *95%CI* [-14.202,22.257]; *b*=-0.100, *SE*=3.296, *95%CI* [-6.606,7.405]). The full model explained 55.40% of the variance in W3-anxiety (*F*(7,35)=6.211, *p*<0.001, R^2=0.554).

The double mediation of W3-depression (**Figure 7(B)**) revealed that rlPFC$_{CT}$ positively predicted W2-depression (*b*=49.163, *t*(37)=3.248, *p*=0.003, R^2=0.248), however, it did not directly predict W3-self-blame (*b*=0.286, *t*(36)=0.348, *p*=0.730) nor W3-depression (*b*=-2.889, *t*(35)=-0.217, *p*=0.829). The total effect of rlPFC$_{CT}$ on W3-depression was significant (*b*=39.625, *t*(37)=2.251, *p*=0.030), but not the full indirect path via W2-depression and W3-self-blame (*b*=10.997, *SE*=8.982, *95%CI* [-4.518,31.215]). Furthermore, W2-depression was a significant positive predictor of the W3-self-blame (*b*=0.032, *t*(36)=4.103, *p*<0.001) and W3-depression (*b*=0.601, *t*(35)=3.902, *p*<0.001). The relationship between W3-self-blame and W3-depression was significant (*b*=6.927, *t*(35)=2.574, *p*=0.015), however W3-self-blame did not mediate rlPFC$_{CT}$ effects on W3-depression (*b*=1.982, *SE*=6.863, *95%CI* [-8.074,19.704]). The relationship between rlPFC$_{CT}$ and W3-depression was significantly mediated by W2-depression (*b*=29.535, *SE*=13.171, *95%CI* [6.407,58.503]). The full model explained 68.86% of variance in W3-depression scores (*F*(7,35)=11.056, *p*<0.001, R^2=0.689).

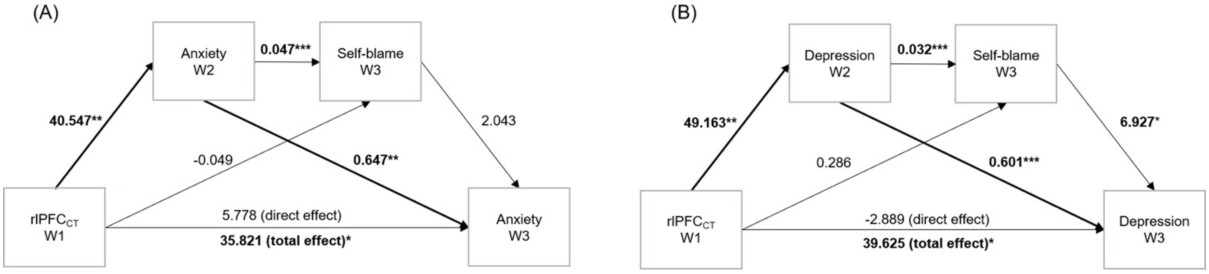

Figure 7. Mediation models investigating the relationship between rlPFC$_{CT}$ at W1 and mental well-being scores at W3. (**A)** Anxiety at W2 mediates the effect of rlPFC$_{CT}$ at W1 on anxiety scores at W3 (*b*=26.215, *SE*=11.651, *95%CI* [8.400,54.076]). **(B)** depression scores at W2 mediate the association between rlPFC$_{CT}$ at W1 and depression at W3 (*b*=29.535, *SE*=13.171, *95%CI* [6.407,58.503]). Significant mediations are depicted as bold paths; *p<0.05, **p<0.01, ***p <0.001.

All data extracted for the relevant brain structures is provided in **Supplementary Table 2.4**. We further provide data from a child group which was part of the larger study (Borbás *et al.*, 2021). This data set was too small for the here employed models but is provided in the **Supplementary Children's Data** section to further possible future pooled data analytic approaches.

Discussion

During the first year after Covid-19 onset anxiety and depression levels varied significantly with different peaks during the assessment period. We demonstrate that adaptive strategies are more frequently employed when dealing with emotions, maladaptive strategies, however, explain most of the variance in negative mental health outcomes during the first year of the pandemic. Overall, the use of adaptive strategies was associated with reduced anxiety, but not depression, while maladaptive strategies were associated with elevated levels of both. The employment of rumination, acceptance, positive reappraisal, refocus on planning and putting into perspective varied throughout the first year after Covid-19 onset. Rumination mediated the association between cortical thickness in right lPFC assessed prior to the start of the pandemic and mental health in the first months after Covid-19 onset. Mental well-being at the end of 2020 was, however, more strongly mediated by early correlates of mental well-being during the pandemic.

Mental well-being during the first pandemic year

Anxiety was highest after the onset of Covid-19 in Switzerland, was decreasing throughout the first months but increased again significantly towards the end of the year. This trajectory might reflect an alarmed state and uncertainty at first followed by an adaptation effect (Vinkers et al., 2020). However, though varying in intensity the prolonged negative experience may have led to a recurring increase in anxiety towards the end of the first pandemic year. Similarly, depression score initially increased then decreased with a recurring increase at the end of the first pandemic year. At the start of the pandemic, 34.88%/20.93% of all participants reported clinically significant levels of anxiety or depression, respectively, and 48.84%/20.93% at the end of the pandemic year. Notably, prior research independent of the pandemic has noted seasonal effects for depressive symptoms in the general population (Oyane et al., 2008). Consequently, the here observed significant increase in anxiety and depression scores towards the end of the year may have similarly been influenced by factors other than those associated with the pandemic. Anxiety and depression scores in our participants during the first months after Covid-19 onset are comparable to larger-scale investigations (de Quervain, 2020; González-Sanguino et al., 2021; Loosen et al., 2021; Pieh et al., 2021; Robinson and Daly, 2021; Salfi et al., 2021). Moreover, although the current study did not assess anxiety and depression prior to Covid-19, heightened scores have been observed worldwide in reports assessing mental health prior to and after Covid-19 onset retrospectively and prospectively (de Quervain et al., 2020; Ettman et al., 2020). Contrary to our reports, some longitudinal studies reported a decline or stagnation for symptoms of anxiety and depression towards the end of the first pandemic year (Loosen et al., 2021; Pieh et al., 2021; Salfi et al., 2021). Such differences may be due to assessment timeframe, local restrictions, population studied or questionnaires used.

Emotion regulation strategy use and mental well-being

Over the course of the first pandemic year the use of some emotion regulation strategies remained relatively constant, while the employment of others varied. Significant variations over time were observed for various adaptive emotion regulation strategies (i.e., acceptance, positive reappraisal, refocus on planning and putting into perspective) and one maladaptive strategy (i.e., rumination). A higher variability in the use of adaptive strategies depending on situational context has been previously reported in cross-sectional studies (Aldao and Nolen-Hoeksema, 2012). In this context we further demonstrated that adaptive strategies were employed more often than maladaptive ones, however, variations in maladaptive strategy use were most strongly linked to worse mental well-being.

Some cognitive emotion regulation strategies were identified as significant predictors of mental health. Positive reappraisal had a buffering effect, while rumination aggravated symptoms of anxiety and depression during the early phase. Reassigning positive meaning to challenging events (positive reappraisal) has previously been reported to precede higher well-being (Garnefski and Kraaij, 2006; Haga et al., 2012; Nowlan *et al.*, 2015) and is recognized in different treatment programs (Beck, 2005; Gratz et al., 2015). Anxiety levels at the end of 2020 were predicted by self-blame only, while depression scores were predicted by self-blame, rumination and refocus on planning. Interestingly, increased use of all three strategies, including refocus on planning, which is usually considered an adaptive strategy, preceded higher depression scores. This is in line with prior research indicating that the effectiveness of specific adaptive strategies may depend on context, including length and nature of the stressful situation experienced (McRae, 2016; Kobylińska and Kusev, 2019). It has been suggested that in situations with low controllability problem-focused strategies used to solve an adverse situation might not be adaptive (Lazarus, 1993). Contrariwise, the use of emotion-focused strategies that aim at changing the emotional state experienced is advised (Troy et al., 2013; Haines et al., 2016). It may thus be hypothesized that the problem-focused strategy of refocus on planning is less adaptive, because minimal control of pandemic circumstances exists. Our data indicates that across the whole group the use of refocus on planning as an emotion regulation strategy was highest shortly after pandemic onset, but less common towards the end of 2020. This might indicate that the negative effects of refocus on planning on mental health observed at the end of the first pandemic year, were driven by a few individuals unable to adapt.

Mediating effects of brain structure and emotion regulation strategy use

Structural brain characteristics assessed prior to pandemic onset were hypothesized to be linked to emotion regulation strategy use consequently mediating levels of anxiety or depression. Bilateral lPFC (gray matter volume or thickness) and amygdala (gray matter volume) were considered, however, only right lPFC thickness remained a significant predictor. Cortical thickness predicted psychological well-being by mediation through rumination at the start and through prior mental well-being at the end of the first pandemic year. LPFC is commonly implicated in cognitive control processes, including emotion regulation (Ochsner et al., 2012; Kohn et al., 2014; Raschle et al., 2019), and altered in clinical disorders, including anxiety or depression (Brühl et al., 2014). While supported by functional (Goldin et al., 2008; Ochsner et al., 2012; Kohn et al., 2014; Raschle et al., 2019) and structural neuroimaging evidence (Kühn et al., 2011; Vijayakumar et al., 2014; Ferschmann et al., 2021), the precise direction of findings remains under investigation and differences in reports may be due to age or group characteristics studied. Greater lPFC cortical thinning was reported during adolescence paralleling an increased use of reappraisal (Vijayakumar et al., 2014; Ferschmann et al., 2021). Furthermore, the choice of emotion regulation strategy studied might impact outcome (Kühn et al., 2011). Our findings associating higher right lPFC thickness and maladaptive strategy use with worse mental health outcomes is in line with meta-analytic evidence investigating rumination and PFC volume in healthy participants (Kühn et al., 2012).

In the present analyses, rumination mediated the relationship between lPFC thickness and anxiety and depression levels in the early phase of the pandemic. The involvement of lPFC functioning in depression (Galynker et al., 1998; Koenigs and Grafman, 2009) and anxiety (Ball et al., 2013) has previously been reported and prolonged depressive episodes and heightened anxiety have been associated with frequent use of rumination (Harrington and Blankenship, 2002; Sarin et al., 2005).

Double mediation models revealed a positive indirect link between right lPFC thickness and mental well-being at the end of 2020 via mental well-being assessed during the first months after pandemic onset. There was no direct association between cortical thickness assessed prior to Covid-19 onset and scores of anxiety or depression at the end of 2020. Additionally, early markers of well-being, as assessed during the first months after pandemic onset in Switzerland, predicted well-being at the end of the year better than individual predispositions (i.e., brain structure) or momentary emotion regulation strategy use. This is in line with Shanahan et al. (2020) reporting that emotional distress during the pandemic is best predicted by emotional distress prior to Covid-19. Furthermore, Brehl and colleagues (2021) demonstrated that anxiety scores during the pandemic were best predicted by a combination of pre-pandemic trait anxiety and maladaptive strategy use.

Limitations

Despite an extensive within-person data collection, the present findings should be interpreted with caution given the relatively small number of participants. Especially in mediation models, small sample sizes are associated with low power and the possibility for exceeding the recommended 5% for Type I error rate (Koopman et al., 2015; Liu and Wang, 2019). To reduce the conducted tests, an average score over six assessment points within W2 was used for the multiple regression and mediation models. Although we report varying effects of emotion regulation strategies on mental health depending on context, larger longitudinal studies are needed to inform about finer-grained time-dependent contextual changes.

Pre-pandemic clinical assessments were not available for all participants, therefore not allowing us to report on changes in anxiety and depression levels or to consider pre-pandemic health in the mediation models. Furthermore, since the global pandemic was experienced by all, no control group is available to deduce to which extent fluctuations in mental health were the consequence of Covid-19 and related restrictions. Additionally, the population studied includes a higher number of female participants. Females and males may be affected differently by stress associated with Covid-19 (Kwong et al., 2020) and the current group did not allow a balanced investigation or assessment of sex-specific effects.

Future studies may further investigate connectivity measures between cortical and limbic regions supporting emotion regulatory functions and investigate their association to successful emotion regulation abilities and mental health to enhance our understanding of the precise mechanisms impacting well-being. Lastly, data acquisition and analysis were not pre-registered due to the rapid response to capture and inform about the early effects of the pandemic-related circumstances.

Conclusions

The experience of prolonged negative life events such as a global pandemic can have a negative effect on mental health. Overall, the use of adaptive emotion regulation strategies was positively associated with mental well-being, while maladaptive strategies were negative for participants' mental health. While first evidence for contextual considerations were identified (e.g., varying effects of certain strategies across time), further research is needed. Our findings underline the potential of interventions minimizing maladaptive emotion regulation use in response to negative life events. Our results suggest that prefrontal cortical thickness assessed prior to the pandemic and emotion regulation strategies used after Covid-19 onset influence mental well-being during the pandemic. Due to substantial personal and societal costs associated with mental health disorders, such as anxiety and depression, an early identification of risk factors for the development and biological and psychological markers for treatment response are of great importance.

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Disclosure

The authors report no biomedical financial interests or potential conflicts of interest.

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Supplementary Material is provided in Appendix A.

6. Discussion

Within this dissertation my central aim was to study the neural correlates of theory of mind processing at different developmental stages, develop a theory of mind task suitable for neuroimaging in children and explore how socioemotional skills captured neurally and behaviorally relate to measures of well-being during challenging life circumstances, such as the Covid-19 pandemic.

6.1. General synopsis

Study I aimed to inform about current knowledge of the neural correlates of theory of mind in children and adolescents. Potential similarities and differences in comparison of children and adolescents to adults were further tested through our systematic literature review and meta-analysis. Generally, large overlaps were observed in the neural correlates of mentalizing across adults, adolescents, and children for brain regions including temporoparietal junction, precuneus and middle medial prefrontal cortex. Adults furthermore recruited prefrontal areas during mentalizing. The considerable overlap in neural activation during mentalizing in all age groups reflects an early specialization of the mentalizing network, corroborating previous findings (Bowman et al., 2019; Gweon et al., 2012; Hyde et al., 2018; Richardson et al., 2018; Richardson & Saxe, 2020).

The comprehensive review of literature provided a solid foundation for **Study II**, which enabled the development and evaluation of a novel theory of mind task appropriate for children and to be conducted within the scanner environment. More specifically, the review process enabled an extensive overview of existing mentalizing tasks that are suitable for use within fMRI experiments. By weighing advantages and drawbacks of the individual paradigms, we decided to create a non-verbal, cartoon story-based mentalizing task allowing the study of affective and cognitive theory of mind processing, with the possibility of collecting explicit answers within the scanner. After task conceptualization and design, the *Cognitive and Affective Theory of Mind Cartoon Task* (CAToon) was evaluated in **Study II**. Behaviorally, CAToon was solved reliably in children of five years of age and older. Neurally, activation in bilateral temporoparietal junction, precuneus, posterior cingulate, bilateral middle and superior temporal gyri and poles, and medial prefrontal cortex was observed across all ages (7- 39 years), which was consistent with previous meta-analytic evidence (Molenberghs et al., 2016; Schurz et al., 2013; Van Overwalle, 2009) including ours in **Study I** (Fehlbaum et al., 2021).

Study II thus describes the successful development and implementation of the CAToon task, rendering it feasible for future pediatric studies employing fMRI.

In **Studies III** and **IV**, sixty-nine participants (including twenty-six mother-child dyads), all of whom previously participated in neuroimaging studies of our laboratory, reported on their mental well-being and psychosocial functioning during the first year following the Covid-19 pandemic onset in Switzerland (six assessments in the first 11 weeks, and a final one after 10 months). We examined the association between structural or functional neural markers of socioemotional processing measured prior to the pandemic and well-being during the pandemic. In adults, several mental health markers (e.g., depression, anxiety, burden of caregiving in mothers) reached clinically significant levels and were highest during the initial phase of the pandemic, but decreased or followed non-linear trends later, rising again at the end of 2020. Children did not display more behavioral or emotional problems in the first months following the onset of Covid-19 in Switzerland compared to pre-pandemic levels, however there was great interindividual variability and mood varied significantly. Moreover, mood and behavioral and emotional problems in children were predicted by mothers' mental health. An increased neural activation during mentalizing (assessed prior to Covid-19) was associated with the development of fears about contamination and illnesses across all participants, including adults and children. Furthermore, increases in neural activation during mentalizing observed prior to the pandemic were linked to an elevated level of experienced burden of caregiving in mothers after the onset of Covid-19. To identify factors serving as a potential buffer against adverse psychological effects, emotional regulation strategy use was investigated. There was great variation in the use of emotion regulatory strategies, and the effect of specific strategies on mental health depended on the phase of the pandemic year. Finally, greater cortical thickness measured prior to Covid-19 in emotion regulatory lateral prefrontal cortex was indirectly connected to worse mental health outcomes during the pandemic via rumination, a maladaptive emotion regulation strategy. In the following sections key findings and their implications are discussed comprehensively. A critical view of the strengths and caveats of each study and potential future directions are further laid out below.

6.2. Neural correlates of theory of mind processing in children, adolescents, and adults

Findings on the neural correlates of theory of mind in adults have previously been reported in different meta-analyses (Molenberghs et al., 2016; Schurz et al., 2013; Van Overwalle, 2009). However, no meta-analytic review to date has targeted neural correlates of mentalizing in developmental groups, and there are only a few neuroimaging studies directly comparing developmental and mature theory of mind processing (Kobayashi et al., 2007; Richardson et al., 2018). Within **Study I** we provide a first systematic meta-analysis of theory of mind-related neural correlates including fMRI studies in children, adolescents, and adults. In addition to summarizing findings in the individual age categories (children, adolescents, and adults), we have conducted conjunction and contrast analyses, allowing us to uncover overlapping and distinct activation patterns.

According to our findings, adults, adolescents, and children share common activation increases in three key regions of the mentalizing network, namely medial prefrontal cortex, precuneus and right temporoparietal junction. Teasing apart cohort-specific increases in neural activation, we observed that in adolescents (12 years or older) left temporoparietal junction, anterior inferior and middle temporal cortices were recruited beyond the areas already activated in children younger than 12 (i.e., middle medial prefrontal cortex, precuneus and right temporoparietal junction) during mentalizing. As such, adolescents' activation pattern was more similar to that of adults. The adult group displayed the most extensive activation pattern, including bilateral inferior, middle, and superior frontal gyri, insula, and occipital pole in addition to the shared areas.

The development of the neural network for mentalizing has been associated with the development of higher-order cognitive skills, including improvements in working memory, attention, inhibitory control, and mnemonic processes (Carlson et al., 2002; Müller et al., 2012; Scott & Baillargeon, 2017). Such higher-order cognitive functions are primarily supported by late-developing structures of the frontal cortex (Gogtay & Thompson, 2010; Simmonds et al., 2017), including inferior and middle frontal gyri, and medial superior frontal cortex (Boisgueheneuc et al., 2006; Hampshire et al., 2010; Japee et al., 2015; Leung et al., 2002; Nachev et al., 2008). These correspond to areas identified uniquely in adults during mentalizing within our current meta-analysis. The novel meta-analytic evidence emerging from **Study I** reflects the development of basic theory of mind skills very early in life followed by a prolonged specialization process through adolescence into adulthood. This trajectory has been observed by a handful of neuroimaging studies (Gweon et al., 2012; Moraczewski et al., 2018; Richardson et al., 2018) and several behavioral paradigms (Blakemore, 2008; Knudsen & Liszkowski, 2012; Korkmaz, 2011) assessing the development of ToM.

6.3. CAToon – a novel tool for measuring affective and cognitive mentalizing in children

In **Study II** I presented the development and successful implementation of a novel MRI-compatible cartoon task assessing affective and cognitive theory of mind processing in children and healthy young adults. In CAToon, participants were asked to complete cartoon stories by choosing from three optional story endings. Outside of the fMRI scanner all children (ages 3-13) solved the task above chance level, however we observed a significant rise in skill levels in children ages five and older. The here observed improvement in five-year-old children corresponds to previously established discontinuity in performance around this age in behavioral studies (Callaghan et al., 2005; Wellman et al., 2001). Accordingly, we suggest the use of CAToon in the fMRI starting at the age of five years.

Study II also confirmed that the CAToon task elicited neural activation patterns typically observed during mentalizing in children and adults, including the medial prefrontal cortex, bilateral temporoparietal junction, middle and superior temporal gyri and precuneus (Molenberghs et al., 2016; Schurz et al., 2014; Van Overwalle & Baetens, 2009). In accordance with **Study I**, we here observed more extensive activation patterns in adults in frontal areas, occipital and insular cortices. Furthermore, distinct activation patterns emerged when comparing affective versus cognitive trials, with affective ToM being uniquely associated with the anterior part of the precuneus extending into the posterior cingulate cortex, as well as within the cuneus and orbitofrontal cortex, corroborated by previous findings of specific activation patterns for affective ToM (Hynes et al., 2006; Schlaffke et al., 2015; Shamay-Tsoory et al., 2010; Völlm et al., 2006). On the contrary, cognitive trials were linked to posterior parts of the precuneus, parahippocampal gyrus, hippocampus, and right insula, adding to previous findings reporting comparable activation increases in the dorsomedial prefrontal cortex, cuneus, bilateral temporoparietal junction and middle superior temporal gyri (Schlaffke et al., 2015).

We further tested whether mentalizing-related neural activation was also elicited during the passive parts of the CAToon task, i.e., during the phase where participants watched three consecutive images of the story without providing behavioral responses. In neuroimaging, a passive paradigm requiring no behavioral response from participants can allow for the inclusion of very young participants (Cantlon & Li, 2013; Moraczewski et al., 2018; Richardson et al., 2018; Richardson & Saxe, 2020). Interestingly, our follow-up analyses considering only the passive parts of the CAToon task yielded robust activation similar to the pattern observed during the complete trial (which included behavioral responses of the participants). Therefore, future neuroimaging studies might employ CAToon as a passive paradigm to open new avenues assessing neural activation during mentalizing already in preschoolers.

Generally speaking, studying the neural underpinnings of mentalizing can add valuable information to existing behavioral findings as it holds the potential to capture hidden mechanisms not evident in behavioral observations. For example, neural pattern and activation magnitude during mentalizing does not differ in children who consistently fail behavioral false belief tasks versus those who succeed (Richardson et al., 2018). Such a discrepancy between neural activation and behavioral performance calls for the joint use of neuroimaging and behavioral measures. A combined approach might enable a more comprehensive understanding of the development of mentalizing.

6.4. Mental health during Covid-19 – factors of risk and resilience

The unforeseen spread of Covid-19 and resulting restrictions allowed the examination of behavioral and neural correlates of socioemotional skills and their relationship with psychological well-being during a stressful life event, here imposed by the Covid-19 pandemic. While **Studies I & II** provided a view into the normative neural development of mentalizing in different age groups, **Studies III & IV** offer a perspective on how socioemotional skills, such as mentalizing or emotion regulation, are associated with psychological well-being. Importantly, our studies deliver a comprehensive approach by combining neural and behavioral characteristics in the exploration of potential risk and resilience factors.

We gathered detailed information in 69 participants during eleven weeks after Covid-19 onset in Switzerland by sending out six bi-weekly online surveys over the course of eleven weeks from March to May 2020. A follow-up survey was added in December 2020, after nine months of initial onset of Covid-19. Baseline testing prior to Covid-19 onset included structural and functional MRI (e.g., CAToon task developed in **Study II**).

In **Study III** we assessed mother and child well-being during the first months after Covid-19 onset (including restrictive measures such as school closures, home office recommendation, only essential shops open, travel restrictions and social distancing). We observed moderately elevated levels of caregiver burden experienced by the mothers initially, which was significantly decreasing throughout the eleven-week assessment phase. As we have not collected parental burden prior to the pandemic we cannot state that burden rose significantly due to the introduction of restrictions, however studies including pre-pandemic measures report significant increases in parental stress during Covid-19 (Calvano et al., 2021; Miller et al., 2020). Based on mothers' reports, children's emotional and behavioral problems, averaged over the first eleven-weeks phase, did not significantly differ from pre-Covid-19 levels, however there was a significant decrease of emotional and behavioral problems across the eleven weeks after Covid-19 onset (between March and May 2020). Experienced burden of the mothers was a significant predictor of children's emotional and behavioral problems and mothers' depressive symptoms predicted children's self-reported mood. Our findings highlight the increased importance of systemic approaches when offering support to children or families because of the critical role of dyadic effects, shown to play a fundamental role in crises (Juth et al., 2015; Lambert et al., 2014).

Starting at school age, peers represent an increasingly important point of reference (Arndt, 2012). Notably, the Covid-19 restrictions in place limited contact with peers during our 11-week-survey. In **Study III** we observed, that meeting friends had a buffering effect on children's mood. This quantitative finding was further corroborated by qualitative data derived from children's subjective reports. 'Not seeing friends or relatives' was reported most frequently (36.30%) as a negative factor by the children during the time of school closure. Moreover, after returning to school an overwhelming majority of open answers (80.65%) were thematizing 'friends' as the best thing about being at school again, and the remaining 19.35% of answers also mentioned some social contacts as a positive factor. Findings presented within this thesis, along with further evidence (Chu et al., 2021; Idoiaga Mondragon et al., 2021; Morgül et al., 2020) support policies striving to keep schools open when possible or enabling opportunities of meeting peers in safe environments during crises such as the Covid-19 pandemic.

Furthermore, the link between functional neural correlates of mentalizing measured prior to the onset of Covid-19 and mental health outcomes during the pandemic was investigated. Better perspective-taking abilities have been previously presented as both a protective factor (Schwarzer et al., 2021; Wells et al., 2020) but also as a potential risk factor (Manczak et al., 2016; Tollenaar & Overgaauw, 2020) for physical and mental health. In our study a significant link was established between higher neural activation during mentalizing in right temporoparietal junction (measured prior to the onset of Covid-19) and increases in mothers' caregiver burden during the pandemic. Additionally, elevated neural activation during mentalizing in right dorsolateral prefrontal cortex was associated with heightened fear of contamination or illnesses. Our findings are thereby in line with studies demonstrating that heightened perspective-taking can lead to elevated physiological and psychological stress (Manczak et al., 2016; Tollenaar & Overgaauw, 2020). Notably, the studies of Manczak and colleagues (2016), and Tollenaar & Overgaauw (2020) employed behavioral measures of mentalizing and empathy to predict biological markers of stress (i.e., inflammation markers, cortisol level, and heart rate reactivity), while our study assessed mentalizing neurally and psychological outcomes behaviorally. Future studies might explore an approach assessing both, predictor and outcome on a physiological and behavioral level.

In **Study IV** we tested trajectories of adult anxiety, depression and emotion regulation strategy use measured repeatedly at seven occasions. We further assessed whether specific emotion regulation strategies were affecting anxiety and depression at the onset of Covid-19 in Switzerland or ten months later. We expected adaptive strategies, usually linked to better mental health (Garnefski et al., 2001), to have a buffering effect on anxiety and depression. Furthermore, we were interested in examining the relationship of emotion regulatory structural brain features measured prior to the pandemic and emotion regulation strategy use and mental health during Covid-19.

In adults, anxiety was above the clinically significant level shortly after the onset of Covid-19 in Switzerland, followed by a decrease during the first eleven weeks of our assessment, but symptoms significantly increased again towards the end of the pandemic year. Depression levels in adults followed a similar pattern, with decreasing depression levels after the fourth week of Covid-19 onset but increasing again at the end of the year. The initial decrease of symptoms might reflect an adaptation effect to a stressful situation as a way of coping (Lazarus, 1966; Loosen et al., 2021) in addition to more relaxed restrictions toward the end of May. A rise in symptoms at the end of the year has also been reported by Dale and colleagues (2021), who observed declining mental health during the Christmas period compared to levels reported during the first lockdown (directly after Covid-19 onset) or levels before the pandemic (Dale et al., 2021). Contrarily, larger-scale investigations and meta-analyses of mental health during the Covid-19 pandemic do not corroborate this trajectory, rather observing stagnation or decline of symptoms in the long run (Loosen et al., 2021; Pieh et al., 2021; Salfi et al., 2021). Such differences in findings can occur depending on questionnaires administered, populations included, the exact timeframe of the studies or restrictions in place. I concur with the idea put forth by Dale and colleague (2021), that adhering to rules and recommendations of the government put in place around Christmas, a holiday centering on community and togetherness, was an increased burden in addition to stricter regulations and elevated levels of positive cases.

By investigating emotion regulation skills in **Study IV,** we were aiming to identify factors of resilience during the pandemic. Interestingly, only one adaptive strategy (out of five), namely positive reappraisal served as a buffer for anxiety and depression, and only in the early pandemic phase (March-May 2020). At the end of 2020 no adaptive strategy buffered negative effects, in fact, the use of refocus on planning (an adaptive strategy) predicted higher depressive scores. On the other hand, maladaptive strategies served as risk factors explaining a high variance in changes of anxiety and depressive symptoms. At the beginning of the year, rumination predicted a decrease in both mental health markers. Towards the end of 2020, the use of self-blame predicted both anxiety and depression, and rumination predicted depression.

Firstly, the here observed negative effect of an adaptive strategy, refocus on planning, supports theories of varying effectiveness of the individual strategies depending on the characteristics of the situation, such as controllability, familiarity, or duration (Aldao & Nolen-Hoeksema, 2012; Kobylińska & Kusev, 2019; McRae, 2016). Refocus on planning is a problem-focused strategy characterized by constructing a plan to influence a situation and setting goals. A problem-focused strategy can work well in controllable situations where employing such a strategy has direct and tangible consequences (Kobylińska & Kusev, 2019). However, an individual has very limited control over the happenings of a pandemic, which might lead to feelings of helplessness and reduced self-efficacy. It seems that, as suggested by Kobylińska and colleagues (Kobylińska & Kusev, 2019) staying flexible in the use of strategies and adjusting to the characteristics of the situation might be the most beneficial way of coping, instead of using a well-rehearsed set of strategies routinely. Based on our findings, interventions should focus on recognizing salient situational features, reducing the use of maladaptive strategies, and replacing them by the situationally fitting strategy. To identify which strategy is successful under which circumstances further investigations are warranted, preferably within a more controlled setting to tease out specific situational cues.

The success of emotion regulation also depends greatly on the neural network supporting this skill set (Kohn et al., 2014; Kühn et al., 2012; Ochsner et al., 2012; Vijayakumar et al., 2014). In **Study IV** we examined how brain structural features in areas subserving emotion regulation (assessed prior to Covid-19) enabled the use of regulatory strategies and thus conjointly affected mental well-being during the pandemic. In the early pandemic phase (March-May 2020) higher cortical thickness in the right lateral prefrontal cortex was associated with declining mental health mediated by the elevated use of rumination. In both anxiety and depression, we observed a complete mediation by the strategy of rumination, reflecting only an indirect relationship between cortical thickness and depressive symptoms.

The relationship of mental health at the end of the pandemic year (December 2020) and higher cortical thickness was completely mediated through the mental health observed between March and May 2020. The use of emotion regulation strategies did not mediate the brain-mental well-being relationship anymore, rendering early mental health correlates to be the best predictors of later mental health outcomes. Although not many studies have investigated the direct link between cortical thickness, emotion regulation, and mental health, greater cortical thickness in the prefrontal cortex has been associated with worse emotion regulation (Vijayakumar et al., 2014) and social anxiety disorder (Brühl et al., 2014; Frick et al., 2013). Such an increase in cortical thickness might be the result of dysregulation or overactivation (Brühl et al., 2014). Moreover, higher cortical thickness may be associated with weakened connection within the emotion regulatory network, affecting emotion regulation skills, however current group size did not allow for follow-up investigations of connectivity.

6.5. Limitations

The four studies presented above yielded thought-provoking findings about socioemotional brain development and how functional and structural brain features link to everyday life and well-being during challenging life events. However, as sound science always considers caveats along with the fortes of the approaches used, I discuss areas of my thesis limiting the quality or interpretation of the presented data in the order of the studies.

6.5.1. Meta-analyses including developmental groups

The reliability of a meta-analysis will always depend on the studies included in the manuscript and is therefore prone to transfer weaknesses of the original studies, such as sampling, data acquisition and processing, or thresholding of the data. Some of these issues are especially challenging in the field of neuroimaging. Our analyses may have been particularly affected by such differences, as we compare studies in adults and children, which tend to be handled differently. For example, there is more movement occurring in children during MRI sessions leading to differences in dealing with motion artefacts but also more lenient thresholds (Meissner et al., 2020; Yerys et al., 2009).

A further inherent weakness of current comparison is the difference in the number of studies in adults (206) versus children & adolescents (22). This limits the interpretation inasmuch that we cannot state with certainty what proportion of the here detected differences between adults and children/adolescents originates from differences in power and what is a true effect. Furthermore, the approach used by our group does not inform about cluster size or the magnitude of the activation, which would be extremely interesting in the comparison we present.

We also face challenges specific for developmental studies. Importantly, our meta-analysis does not inform about developmental effects, as it does not focus on studies following cohorts with repeated measures. Additionally, the distinction between childhood and adolescence should ideally rely on measures beyond chronological age, such as pubertal status (marked by bodily changes) or biological data, but no comparable measures were available in the studies included here.

6.5.2. Creating an fMRI-compatible theory of mind task for children

While we paid particular attention to design a task which is suitable for measuring affective and cognitive theory of mind in the scanner in children, there are some weaknesses to be mentioned. First, the inclusion of an established behavioral theory of mind task would have been ideal to serve as a control. Even though CAToon is eliciting neural activation coherent with mentalizing, an external task would have been interesting to examine whether neural activation was connected to task performance. Such a control task could have further enabled the examination of the meaningfulness of our behavioral data. I am also cautious about the task's ability to differentiate levels of mentalizing performance beyond a certain age. This is partly due to the selected task type. It is genuinely difficult to include items representing higher-order mentalizing (e.g., "A believes that B believes that C believes that D believes that E believes something", (Launay et al., 2015)) in a cartoon task with limited number of stimuli per trial presented. Here, we had to agree to a trade-off between task feasibility for children and the accuracy of the task as a behavioral measure. As we were highly interested in studying the neural development of theory of mind, we decided to select a design best suitable for even the youngest participants inside the scanner.

Second, although CAToon was designed to capture neural activation associated with affective and cognitive mentalizing, the stimuli included are not as cleanly separated as in other experimental tasks. Our cognitive trials also include affective cues, as the characters presented express emotions, similarly to the affective trials. While we created the trials such that to solve the affective trials, the characters' emotions should be most salient, and to solve the cognitive trials the characters' intentions and thoughts would be needed for a correct answer, we cannot exclude that participants relied on emotional cues in both trials. To understand what decision-making mechanisms the task induces, follow-up studies are needed.

6.5.3. Repeated measures during Covid-19

While our repeated collection of data represents a uniquely well-characterized group of individuals, the low number of participants does not provide sufficient power to follow up on more complex models. Although the mediation models presented here were the result of a parameter distribution method less sensitive to alpha and beta errors, I still advise the careful interpretation of the results due to the small group size as well as the unequal distribution of sexes. Also limited by the low power are mother-child associations, which were here examined using regression modeling. Dyadic dynamics would ideally be tested in statistical models allowing for bidirectional effects and accounting for time effects such as the actor-partner interdependence model (Cook & Kenny, 2005; Kenny et al., 2020), which regards the dyad as the unit of the investigation and accounts for the non-independent nature of such data. Additionally, this model would allow to test the stability of an effect over time. Unfortunately, such a model would require a large number of dyads for reliable statements, which was not possible with the 26 dyads included in our Covid-19 study.

The impact of the pandemic has not been subjectively measured in our studies, limiting any interpretation directly associating the pandemic and the observed fluctuations in psychological well-being. Making grounded statements about ‘heightened’ or ‘increased’ mental health symptoms should further be handled with utmost care, as we have not collected mental health data in adults prior to the pandemic corresponding to the data acquired during Covid-19. This is partly due to the recruitment of adult participants from different studies. Comparable data was only available in children.

We have no direct evidence that higher engagement of the mentalizing network truly reflected higher levels of mentalizing in our group. Therefore, the findings associating higher neural activity with better or more mentalizing must be considered with caution. In future studies the addition of a more complex mentalizing task or a task about the propensity to mentalize in different situations would be a great addition to see whether better ‘mentalizers‘, or those who subjectively report more mentalizing behavior, are more affected by adverse life events. Finally, as all data was collected within a relatively small group and in one specific region of Switzerland, the generalizability of presented findings is limited.

6.6. Conclusion & outlook

The investigation of mentalizing has come a long way since the first behavioral task implemented in the study with Sarah, the chimpanzee. Neuroimaging methods have proven to be an excellent complementary approach to behavioral paradigms. Neural evidence emerging from this thesis together with studies from recent years supports an early development of the core mentalizing network in young children, though further specialization continues to take place across adolescence. The unique asset that neuroimaging can add currently is the ability to observe more fine-grained developmental steps preceding behavioral change, as mentalizing-specific neural correlates are present before children pass behavioral tasks (Gweon et al., 2012; Hyde et al., 2018; Moraczewski et al., 2018; Richardson et al., 2018; Richardson & Saxe, 2020).

CAToon, the mentalizing task developed within the framework of this thesis, might be ideal to capture such early neural development of the mentalizing system. In future studies I would be extremely interested to employ CAToon as a passive viewing task with no responses required, thus enabling the investigation of the neural correlates of mentalizing in children younger than five. It would be of further interest to omit instructions in a subgroup of the participants. The removal of instructions would create an implicit paradigm, meaning that the participants are not focusing on specific aspects or working towards a goal during the task. Implicit theory of mind processing is believed to develop early and not depend on complementary skills, such as language or executive functions (Molenberghs et al., 2016). Comparing groups completing CAToon in its current form (including instructions and requiring behavioral response from participants) and as an implicit task could inform about true differences between implicit and explicit ToM processing while using a perfectly matched set of stimuli. Furthermore, studying the developmental trajectory of theory of mind skills by repeatedly scanning children as they age would be an interesting new direction currently missing from the field of mentalizing.

Behaviorally, theory of mind development and performance in children depends greatly on the maturation of executive functions, such as attention, inhibition, or cognitive flexibility (Carlson et al., 2004; Müller et al., 2012; Scott & Baillargeon, 2017). On the neural level the interplay of the mentalizing network and networks promoting complex cognitive processes is a deciding factor in theory of mind skill development (van Buuren et al., 2021). The default mode network, originally associated with activation increases during rest (Biswal et al., 1995; Raichle et al., 2001) and later with introspective focus and social cognitive processes (Gusnard & Raichle, 2001; Nair et al., 2020; Spreng & Andrews-Hanna, 2015) subserves theory of mind processing. A recent study using intrinsic functional connectivity presents first evidence of better mentalizing performance in individuals with higher connectivity between default mode network and frontoparietal/cingulo-opercular networks (networks underlying cognitive control processes, (van Buuren et al., 2021)). An intrinsic connectivity approach includes many advantages, such as stability within an individual independent of the mental state (e.g., different types of tasks or resting), ability to distinguish between individuals highly accurately, and use for brain-behavioral predictions (Finn et al., 2015; Larabi et al., 2021; Lin et al., 2020). Therefore, future studies might delve into this comprehensive approach potentially resulting in more accurate and stable neural profiles of mentalizing.

The investigation of familial effects in the neural development of socioemotional skills is of further interest. Disentangling genetic and contextual effects influencing skill development is a novel avenue in developmental neuroscience. First studies examined structural (Foland-Ross et al., 2016; Yamagata et al., 2016) and functional (Colich et al., 2017; Silvers et al., 2021; Takagi et al., 2021) neural similarity in parent-child dyads, revealing specific transmission patterns of some traits. Our neural data in children and mothers allows for such investigations in the future, examining for example functional neural similarity in mother-child dyads during CAToon task performance. Additionally, testing how neural interpersonal similarity in dyads is linked to psychosocial well-being in children is scarcely researched, despite its potential to inform about transgenerational pathways of psychosocial functioning.

In conclusion, socioemotional skill development is crucial for an individual’s well-being throughout the life course (Atzil et al., 2018). Thus, research furthering the understanding of socioemotional skills creates substantial value for the community, by informing about developmental pathways and possible preventive or interventive approaches. Combining biological and behavioral markers and considering the individual as part of a complex social system can further a comprehensive understanding of how socioemotional skills develop and in what way they relate to momentary and life-long well-being.

Declaration by Candidate

I declare that this dissertation has been composed independently. All research articles have been published in or submitted to peer-reviewed journals and were written in collaboration with the listed co-authors. All citations are referenced and only the mentioned sources were used.

The dissertation includes the following articles:

Fehlbaum, L., **Borbás, R.,** Paul, K., Eickhoff, S.B. & Raschle, N. (2021). Early and late neural correlates of mentalizing: ALE meta-analyses in adults, children and adolescents. *Social Cognitive and Affective Neuroscience.*
CRediT: conceptualization, data curation, project administration, writing – review & editing

Borbás, R., Fehlbaum, L. V., Rudin, U., Stadler, C., & Raschle, N. M. (2021). Neural correlates of theory of mind in children and adults using CAToon: Introducing an open-source child-friendly neuroimaging task. *Developmental cognitive neuroscience*, *49*, 100959.
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Borbás, R., Fehlbaum, L., Dimanova, P., Negri, A., Arudchelvam, J., Schnider, C. B., & Raschle, N. (2021). Mental well-being during the first months of Covid-19 in adults and children: behavioral evidence and neural precursors. *Scientific reports,* 11, no. 1 (2021): 1-14.
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Dimanova, P.*, **Borbás, R.***, Schnider, C. B., Fehlbaum, L., & Raschle, N. (2021). Direct and indirect effects of dorsolateral prefrontal cortex and emotion regulation strategy use on mental health during Covid-19. Under review at *Social Cognitive and Affective Neuroscience.*
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Additional articles not included in this dissertation:

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CRediT: writing – review & editing

Menks, W. M., Fehlbaum, L. V., **Borbás, R**., Sterzer, P., Stadler, C., & Raschle, N. M. (2021). Eye gaze patterns and functional brain responses during emotional face processing in adolescents with conduct disorder. *NeuroImage: Clinical*, *29*, 102519.

CRediT: investigation (data collection), visualization, writing – review & editing

Fehlbaum, L. V., Peters, L., Dimanova, P., Roell, M., **Borbás, R**., Ansari, D., & Raschle, N. M. (2022). Mother-child similarity in brain morphology: A comparison of structural characteristics of the brain's reading network. *Developmental cognitive neuroscience*, *53*, 101058.https://doi.org/https://doi.org/10.1016/j.dcn.2022.101058
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Réka Borbás

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Curriculum Vitae

Personal information

Name	Réka Borbás
Birth date and place	July 2, 1992, Szeged (Hungary)
Nationality	Hungary
Languages	English (fluent, C2), German (Goethe-Zertifikat C1), French (basic, B2), Hungarian (native speaker)

Education

09/2007 – 06/2012	Deák Ferenc Bilingual High School, Szeged (Hungary)
09/2009 – 12/2009	Brooks School, North Andover, Massachusetts, USA, Exchange Scholarship
08/2010 – 07/2011	Neue Kantonsschule High School Aarau, Switzerland, Exchange Year
09/2012 – 06/2015	University of Szeged, Hungary, Faculty of Psychology, Bachelor of Arts (BA)
09/2015 – 06/2017	University of Basel, Faculty of Psychology, Master of Science (MSc), Clinical Psychology and Neuroscience
08/2017 –	PhD in Psychology at the University of Basel, Psychiatric University Clinics Basel (UPK), Research Department of the Child and Adolescent Psychiatry, and Jacobs Center for Productive Youth Development at the University of Zurich

Practical experience

Fall 2014	Data collection in an EEG Study: „The interplay of holistic shape, local feature and color information in object categorization “
Spring 2015	Empirical Bachelor Thesis: „The effect of food-related words on anorexia nervosa patients in the lexical decision task “
04/2015	National Student Conference in Debrecen (Hungary), presentation of student project: „The effects of allergic rhinitis on the cognitive functions of athletes and non-athletes.“

09/2015 - 06/2017	Masterproject: „*Behavioural and Neuronal Correlates of Emotion Processing and Emotion Regulation in Psychiatric Patients with Empathy Deficits - an fMRI Project"* Data collection, Data analysis (fMRI and behavioral) at the Research Department of the Child and Adolescent Psychiatry, Basel
07/2016 - 01/2017	Psychology internship (80%) at the psychosomatic ward of the Barmelweid Clinic (Canton Aargau, Switzerland)
03/2017 - 06/2017	Research internship at the Research Department of the Child and Adolescent Psychiatry, Basel, Switzerland
since 04/2017	Supervising and co-supervising and training Master students along with their master projects and master theses.
04/2019 -	Doctoral Research Associate in Developmental Neuroscience at the Jacobs Center for Productive Youth Development (University of Zurich, Switzerland)

Trainings in academia

06/2017	MRI safety certificate, Radiology & Nuclear Medicine Clinic, University Hospital Basel
09/2017 – 12/2017	Structural and functional neuroimaging in Psychiatry (course at the University of Basel)
09/2017	Statistical Parametric Mapping (SPM) course and Computational Anatomy Toolbox (CAT12) course at the Institute of Systems Neuroscience, Hamburg
02/2018 - 05/2018	Exploring Brain Connectivity with Diffusion MRI: Hands-on Processing and Applications to Neuropsychology (course at the University of Basel)
09/2018	Good Clinical Practice (GCP)-Basic course provided by the Department of Clinical Research of the University of Basel

Extracurricular training

02 – 06.09.2019	6th Trifels Summer Summer School: Global Challenges and Systems Thinking

08/2021 – 09/2021	Introduction to Coding, SheCodes Workshop, HTML 5, CSS 3, Javascript ES 6, VS Code
22 – 30.06.2021	*From Knowing Humans to Knowing Data:* workshop and Retreat in Social Data Science funded by the Graduate Campus at the University of Zurich

Publications:

2022	Fehlbaum, L. V., Peters, L., Dimanova, P., Roell, M., **Borbás, R.,** Ansari, D., & Raschle, N. M. (2022). Mother-child similarity in brain morphology: A comparison of structural characteristics of the brain's reading network. *Developmental cognitive neuroscience*, *53*, 101058.https://doi.org/https://doi.org/10.1016/j.dcn.2022.101058
2021	Fehlbaum, L., **Borbás, R.,** Paul, K., Eickhoff, S.B. & Raschle, N. (2021). Early and late neural correlates of mentalizing: ALE meta-analyses in adults, children and adolescents. *Social Cognitive and Affective Neuroscience.*
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	Borbás, R., Fehlbaum, L., Dimanova, P., Negri, A., Arudchelvam, J., Schnider, C. B., & Raschle, N. (2021). Mental well-being during the first months of Covid-19 in adults and children: behavioral evidence and neural precursors. *Scientific reports,* 11, no. 1 (2021): 1-14.
	Menks, W. M., Fehlbaum, L. V., **Borbás, R.,** Sterzer, P., Stadler, C., & Raschle, N. M. (2021). Eye gaze patterns and functional brain responses during emotional face processing in adolescents with conduct disorder. *NeuroImage: Clinical*, *29*, 102519
2020	Raschle, N. M., **Borbás, R**., King, C., & Gaab, N. (2020). The magical art of magnetic resonance imaging to study the reading brain. *Frontiers for Young Minds,* doi: 10.3389/frym.2020.00072

Preprints, under review or in press:

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***shared first authorship**

Peer-reviewed conference presentations, abstracts and posters:

2021	Borbás, R., Dimanova, P., Fehlbaum, L. V., Negri, A., Arudchelvam, J., Schnider, C.B., Raschle, N.M. (2021). Effects of COVID-19 and restrictions on well-being in adults and synchronous psychosocial functioning within mother-child dyads. Presentation at the Paper Symposium: Understanding Dyadic Biobehavioral

Synchrony: Developmental Precursors and Functionsthe; virtual biennial meeting of the Society for Research in Child Development, April 2021.

2020 Borbás, R., Fehlbaum, L. V., Dimanova, P., Raschle, N.M. (2020). Neural correlates of Theory of Mind processing in children, mothers and mother-child dyads. Poster presented at the second Annual Meeting of the Swiss Society for Early Childhood Research (SSECR), November 2020, Online Video Conference.

2019 Borbás, R., Fehlbaum, L. V., Rudin, U., Raschle, N.M. (2019). CAToon – a novel, child-friendly functional neuroimaging task for the assessment of theory of mind. Poster presented at the first Annual Meeting of the Swiss Society for Early Childhood Research (SSECR), Lausanne, November 2019.

2018 Borbás, R., Fehlbaum, L.V., Stadler, C., Raschle, N.M. (2018). Theory of Mind and Language Processing in 7-12-year-olds. Poster presented at the 5th FemNAT-CD General Assembly Meeting, Frankfurt, January 2018.

Borbás, R., Fehlbaum, L.V., Rudin, U., Schnider, M., Grob, C., Stadler, C., Raschle, N.M. (2018). Neural correlates of affective and cognitive Theory of Mind: A novel functional neuroimaging cartoon task for children. Poster presented at the 6th annual Flux Congress, Berlin, August 2018.

Appendices

Appendix A

Supplementary Material to Study IV: Impact of prefrontal cortical thickness and emotion regulation strategy use on Covid-19 mental health:

Supplementary Materials

1. Supplementary Methods

1.1. List of assessments

CBCL: Child Behavior Checklist (Achenbach and Ruffle, 2000); **RPQ**: Relationship Problems Questionnaire (Minnis *et al.*, 2002); **ICU**: Inventory of Callous-Unemotional traits (Essau *et al.*, 2006); **SDQ**: Strength and Difficulties Questionnaire (Goodman, 1997, 2001); **HAWIK-IV**: Hamburg-Wechsler-Intelligenztest für Kinder (fourth version, (Petermann and Petermann, 2008)); **IDS**: Intelligence and Developmental Scale (Grob and Hagmann-von Arx, 2012); **Mood**: own questionnaire (Children were choosing between 5 different smileys to indicate their mood in the last few days, ranging from 1 (very happy) to 5 (sad)); **ERQ:** Emotion Regulation Questionnaire (for adults (Gross and John, 2003) and for children (Gullone and Taffe, 2012)); **PSS**: Parental Stress Scale (Berry and Jones, 1995); **APQ**: Alabama Parenting Questionnaire (Frick, 1991); **BSI**: Brief Symptom Inventory (Derogatis and Melisaratos, 1983); **BSFC**: Burden Scale for Family Caregivers (Graessel *et al.*, 2014); **IRI**: Interpersonal Reactivity Index (Davis, 1980); **YPI**: Youth Psychopathic traits Inventory (Andershed *et al.*, 2007); **STAI-6**: State and Trait Anxiety Inventory (short form, (Laux, 1981)); **K10**: Kessler Psychological Distress Scale (adapted, (Kessler and Mroczek, 1994; Giesinger *et al.*, 2008)); **GHQ**: General Health Questionnaire (Hankins, 2008); CESD-R: Center for Epidemiologic Studies Depression Scale – Revised (Deutsche Fassung, (Lewinsohn *et al.*, 1997; Schmitt, 2016)); **CERQ-s**: Cognitive Emotion Regulation Questionnaire – short version (Garnefski *et al.*, 2007); **Media**: own questions; **Time Outside**: own questions; **FIVE**: the Fear of Illness and Virus Evaluation (credits: Dr. Ehrenreich-May (2020), https://adaa.org/node/5168); **MRI**: Magnetic Resonance Imaging (structural and functional data).

1.2. Behavioral assessments

In adult participants the German short-form of the cognitive emotion regulation questionnaire (**CERQ-s**; (Garnefski *et al.*, 2007)) was employed to assess momentary use of emotion regulation strategies during the early phase of the Covid-19 pandemic (six assessments across

W2) and one more time at the end of the pandemic year (W3). The CERQ-s is a self-report instrument for the assessment of nine different cognitive emotion regulation strategies by means of 18 items, including self-blame, other-blame, rumination, catastrophizing, putting into perspective, positive refocus, positive reappraisal, acceptance and refocus on planning. Two factors can be calculated: adaptive cognitive emotion regulation (based on five strategies: positive refocusing, positive reappraisal, putting into perspective, refocus on planning and acceptance) and maladaptive cognitive emotion regulation (based on four strategies: rumination, self-blame, blaming others and catastrophizing). Mental well-being correlates during the pandemic (W2-W3) were assessed through use of a short-form of the State-Trait Anxiety Inventory (**STAI-6**; (Marteau and Bekker, 1992)) and by the Center for Epidemiologic Studies Depression Scale – Revised (**CESD-R**, German version, (Lewinsohn *et al.*, 1997; Schmitt, 2016)). The STAI-6 is a self-report questionnaire assessing state anxiety at a given moment (STAI-6 total, which is based on 6 items with scores comparable to the 20-item questionnaire, ranging between 20 and 80 (Spielberger, 1970; Bekker *et al.*, 2003), while the CESD-R is a self-report instrument to screen for the presence of depressive symptoms (scores between 0 and 60, based on 20 items (Lewinsohn *et al.*, 1997; Schmitt, 2016)). Additionally, trait emotion regulation skills were assessed once for each wave using the Emotion Regulation Questionnaire (**ERQ**, a behavioral assessment consisting of 10 questions targeting the habitual use of expressive suppression and cognitive reappraisal (Gross and John, 2003; Abler and Kessler, 2009). For children, behavioral and emotional problems were assessed through the Strength and Difficulties Questionnaire (**SDQ**; (Goodman, 1997)), a brief behavioral screening questionnaire filled out by parents to assess psychological adjustment of children and adolescents between 4 to 17 years (Goodman, 2005). 25 items are rated and used to build five subscales. Emotional and peer problems building the “internalizing” subscale, while conduct problems and hyperactivity are grouped into the “externalizing” subscale. The four scales are summed into a total score, reflecting child’s behavioral and emotional problems.

1.3. Structural magnetic resonance imaging (sMRI) data acquisition

Structural T1-weighted MPRAGE data was acquired on a Siemens 3T Prisma MR scanner using 20-channels head coil. Images were obtained applying the following specifics: voxel size: 1.0×1.0×1.0mm; TR=1900ms; TE=3.42ms; TA=4.26; flip angle=9 degrees; field of view=256x256mm, 192 slices with a slice thickness of 1.00mm. Simultaneous multislice acquisition and dummy scans, which were directly discarded, preceded image acquisition and allowed us to account for T1 equilibration effects.

1.4. Structural data quality assurance

Motion is a prevalent issue, particularly in pediatric neuroimaging studies. During the data collection for this study, we adhered to practices suggested for pediatric neuroimaging (Raschle *et al.*, 2009; Raschle *et al.*, 2012; Thieba *et al.*, 2018). This included an age-appropriate training session for the MRI study, ample time for conducting the neuroimaging session and further specifics to make the participants feel comfortable, e.g., offering them the possibility to wear their own MR-safe clothing (instead of a hospital gown), giving them a pre-heated blanket. Furthermore, participants were able to select a cartoon movie or a documentary to watch during structural image acquisition, associated with less movement(Huijbers *et al.*, 2017). For head fixation inflatable pillows were used, moulding ideally to each participant's head shape and minimizing movement possibility.

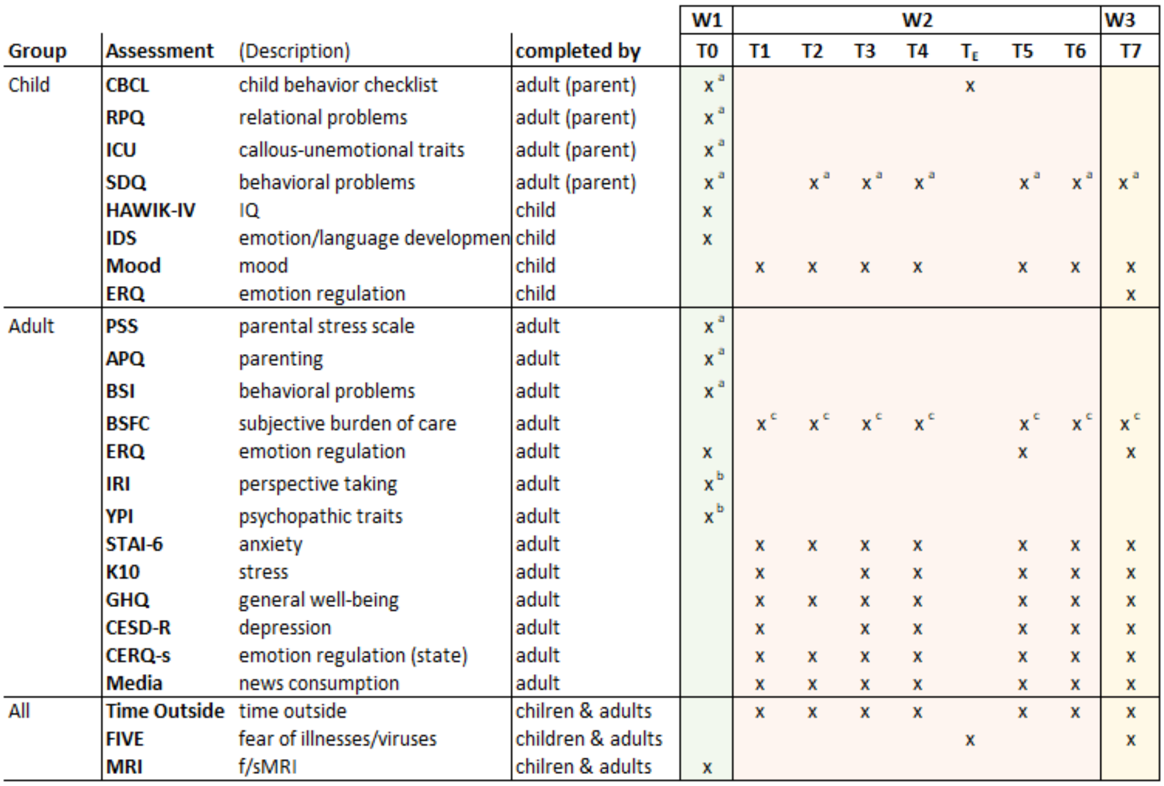
Even though the study protocol was conducted in a way that did not allow for a lot of movement, the data quality of the structural images was visually inspected in axial, coronal and sagittal view slice-by-slice for each participant by one of the three raters (P.D., L.F., T.M.). The visual inspection aimed to exclude scans of insufficient quality or with inaccurate delineation of the white and gray matter. Due to the high quality of the structural data in the reported group, there were no participants whose data was excluded from the conducted analyses.

2. Supplementary Tables

Supplementary Table 2.1. Adults' participation in the online survey and retention rate at each time point across the three assessment waves. Percentages are calculated based on 43 adults taking part in the online study.

Timepoint		Adults	Adults %
W1	T0	60	Baseline
	T1	37	86.05%
	T2	42	97.67%
	T3	41	95.35%
W2	T4	39	90.70%
	T_E	40	93.02%
	T5	29	67.44%
	T6	37	86.05%
W3	T7	37	86.05%

Supplementary Table 2.2. List of assessments conducted across the three data collection waves – before Covid-19 onset (W1), during the first months of the pandemic (March – May; W2) and at the end of the year (W3).



				W1	W2							W3
Group	Assessment	(Description)	completed by	T0	T1	T2	T3	T4	T_E	T5	T6	T7
Child	**CBCL**	child behavior checklist	adult (parent)	x[a]					x			
	RPQ	relational problems	adult (parent)	x[a]								
	ICU	callous-unemotional traits	adult (parent)	x[a]								
	SDQ	behavioral problems	adult (parent)	x[a]		x[a]	x[a]	x[a]		x[a]	x[a]	x[a]
	HAWIK-IV	IQ	child	x								
	IDS	emotion/language developmen	child	x								
	Mood	mood	child		x	x	x	x		x	x	x
	ERQ	emotion regulation	child									x
Adult	**PSS**	parental stress scale	adult	x[a]								
	APQ	parenting	adult	x[a]								
	BSI	behavioral problems	adult	x[a]								
	BSFC	subjective burden of care	adult		x[c]	x[c]	x[c]	x[c]		x[c]	x[c]	x[c]
	ERQ	emotion regulation	adult	x						x		x
	IRI	perspective taking	adult	x[b]								
	YPI	psychopathic traits	adult	x[b]								
	STAI-6	anxiety	adult		x	x	x	x		x	x	x
	K10	stress	adult		x		x	x		x	x	x
	GHQ	general well-being	adult		x	x	x	x		x	x	x
	CESD-R	depression	adult		x		x	x		x	x	x
	CERQ-s	emotion regulation (state)	adult		x	x	x	x		x	x	x
	Media	news consumption	adult		x	x	x	x		x	x	x
All	**Time Outside**	time outside	chilren & adults		x	x	x	x		x	x	x
	FIVE	fear of illnesses/viruses	children & adults						x			x
	MRI	f/sMRI	chilren & adults	x								

[a] filled out by mothers only [b] filled out by adults not part of the mother-child study [c] filled out by parents

Supplementary Table 2.3. Paired-sample t-tests comparing the use of adaptive versus maladaptive emotion regulation strategies at each assessment timepoint.

Adaptive vs maladaptive ($\text{mean}_{\text{adaptive}}$, $\text{mean}_{\text{maladaptive}}$)	*t*(42)	*P*
T1 (5.944, 3.145)	12.768	< 0.001
T2 (5.861, 2.983)	14.372	< 0.001
T3 (5.814, 2.942)	11.787	< 0.001
T4 (5.502, 3.070)	9.114	< 0.001
T5 (5.507, 2.977)	10.770	< 0.001
T6 (5.656, 2.965)	10.678	< 0.001
T7 (5.479, 3.035)	10.607	< 0.001

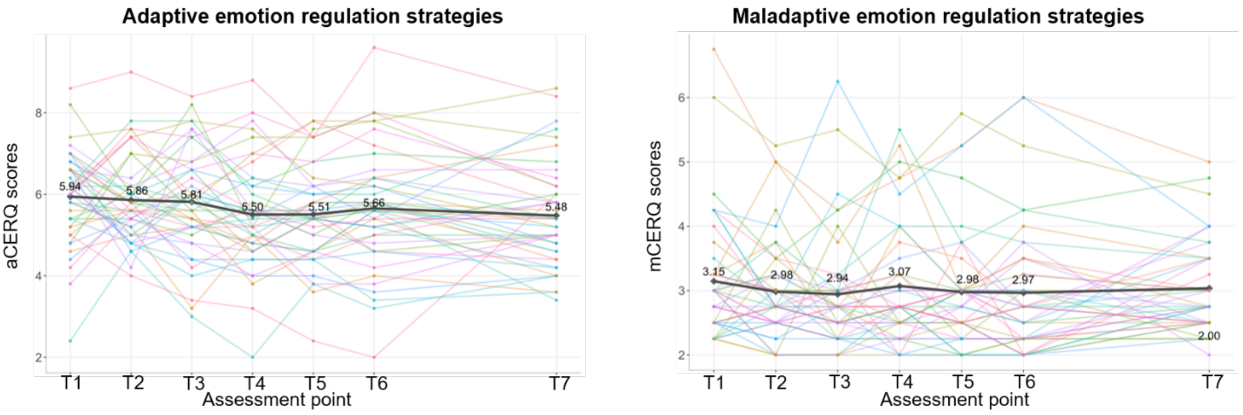
Supplementary Table 2.4. Extracted values of cortical thickness, gray matter volume and eTIV, and eTIV scaled gray matter volume for the bilateral dorsolateral prefrontal cortex and amygdala in adults.

	Cortical thickness		**Gray matter volume**					**Gray matter volume scaled for eTIV**			
Sub-Ject	Right dlPFC	Left dlPFC	Right dlPFC	Left dlPFC	Right Amygdala	Left Amygdala	eTIV	Right dlPFC	Left dlPFC	Right Amygdala	Left Amygdala
1	2.56	2.61	31408.00	30846.00	1944.90	1700.30	1424374.67	0.0221	0.0217	0.0014	0.0012
2	2.48	2.57	32860.00	33406.00	1712.40	1534.90	1666261.63	0.0197	0.0200	0.0010	0.0009
3	2.49	2.57	30188.00	28227.00	1671.10	1537.20	1461502.17	0.0207	0.0193	0.0011	0.0011
4	2.52	2.45	33016.00	31051.00	1759.70	1519.70	1387825.95	0.0238	0.0224	0.0013	0.0011
5	2.74	2.68	31297.00	31002.00	1906.00	1876.90	1424862.25	0.0220	0.0218	0.0013	0.0013
6	2.59	2.55	33326.00	32424.00	1725.90	1532.90	1569744.52	0.0212	0.0207	0.0011	0.0010
7	2.48	2.57	26576.00	32175.00	1461.00	1267.70	1501067.86	0.0177	0.0214	0.0010	0.0008
8	2.47	2.50	29490.00	30186.00	1568.40	1540.70	1557748.84	0.0189	0.0194	0.0010	0.0010
9	2.52	2.62	30779.00	32930.00	1738.50	1525.10	1550550.43	0.0199	0.0212	0.0011	0.0010
10	2.54	2.56	31932.00	32159.00	1836.80	1687.50	1518312.31	0.0210	0.0212	0.0012	0.0011
11	2.43	2.53	30671.00	31609.00	1647.80	1484.10	1554169.16	0.0197	0.0203	0.0011	0.0010
12	2.70	2.71	32192.00	31397.00	1715.70	1640.90	1450465.53	0.0222	0.0216	0.0012	0.0011
13	2.72	2.62	34034.00	36029.00	1913.00	1912.40	1405177.21	0.0242	0.0256	0.0014	0.0014
14	2.55	2.63	31181.00	33170.00	1833.90	1667.50	1506903.99	0.0207	0.0220	0.0012	0.0011
15	2.67	2.65	34680.00	37154.00	1836.00	1785.60	1582015.67	0.0219	0.0235	0.0012	0.0011
16	2.45	2.53	34711.00	36135.00	2113.80	1943.60	1816935.29	0.0191	0.0199	0.0012	0.0011
17	2.61	2.58	36223.00	32457.00	1659.20	1748.20	1568939.00	0.0231	0.0207	0.0011	0.0011
18	2.59	2.48	33195.00	32283.00	1670.20	1374.30	1588034.03	0.0209	0.0203	0.0011	0.0009
19	2.48	2.54	35879.00	34475.00	1875.80	1593.00	1729184.77	0.0207	0.0199	0.0011	0.0009
20	2.39	2.53	29635.00	29554.00	1824.90	1491.90	1604669.46	0.0185	0.0184	0.0011	0.0009
21	2.43	2.49	34851.00	34928.00	2134.30	2115.00	1265018.03	0.0275	0.0276	0.0017	0.0017
22	2.61	2.75	39733.00	38682.00	1977.60	1748.20	1870655.59	0.0212	0.0207	0.0011	0.0009

23	2.67	2.66	33010.00	33493.00	1739.40	1802.50	1480663.47	0.0223	0.0226	0.0012	0.0012
24	2.76	2.84	31327.00	32315.00	1765.00	1665.20	1256853.45	0.0249	0.0257	0.0014	0.0013
25	2.81	2.80	37581.00	36051.00	1753.50	1689.40	1662165.67	0.0226	0.0217	0.0011	0.0010
26	2.68	2.71	33721.00	33822.00	1895.00	1719.30	1801512.83	0.0187	0.0188	0.0011	0.0010
27	2.48	2.64	29252.00	30898.00	1444.80	1404.80	979371.09	0.0299	0.0315	0.0015	0.0014
28	2.49	2.57	37567.00	40464.00	1886.10	2045.90	1757813.06	0.0214	0.0230	0.0011	0.0012
29	2.60	2.71	38628.00	26815.00	1721.70	1600.70	1358131.02	0.0284	0.0197	0.0013	0.0012
30	2.61	2.71	44983.00	47219.00	2283.40	2095.70	2008134.04	0.0224	0.0235	0.0011	0.0010
31	2.55	2.62	31965.00	33804.00	1819.00	1698.40	1557128.26	0.0205	0.0217	0.0012	0.0011
32	2.44	2.45	36449.00	36569.00	1868.30	1702.50	1781798.97	0.0205	0.0205	0.0010	0.0010
33	2.51	2.55	31819.00	34302.00	1540.20	1424.40	1320862.97	0.0241	0.0260	0.0012	0.0011
34	2.78	2.81	37162.00	36995.00	2142.30	1813.70	1716132.33	0.0217	0.0216	0.0012	0.0011
35	2.82	2.78	41844.00	38329.00	2004.00	1967.60	1889434.18	0.0221	0.0203	0.0011	0.0010
36	2.62	2.61	37783.00	37240.00	1831.20	1755.80	1385558.37	0.0273	0.0269	0.0013	0.0013
37	2.81	2.75	46039.00	45116.00	2282.80	1891.10	1815779.51	0.0254	0.0248	0.0013	0.0010
38	2.67	2.70	34644.00	36794.00	1934.80	1758.60	1576935.34	0.0220	0.0233	0.0012	0.0011
39	2.49	2.52	39276.00	41428.00	1949.60	1858.20	1892200.58	0.0208	0.0219	0.0010	0.0010
40	2.56	2.56	34986.00	36166.00	1952.60	1609.60	1790631.89	0.0195	0.0202	0.0011	0.0009
41	2.64	2.56	37140.00	34942.00	1820.50	1556.80	1616073.57	0.0230	0.0216	0.0011	0.0010
42	2.64	2.79	49091.00	37502.00	2025.90	2003.90	1729500.64	0.0284	0.0217	0.0012	0.0012
43	2.76	2.78	52101.00	49700.00	2207.70	2062.10	1979336.21	0.0263	0.0251	0.0011	0.0010

dlPFC: dorsolateral prefrontal cortex; eTIV: estimated total intracranial volume

3. Supplementary Figures



Supplementary Figure 3.1. Individual variation of adaptive and maladaptive emotion regulation strategies over seven timepoints after Covid-19 onset.

4. Supplementary Children's Data

4.1. Participants

Along with the adults' data, we have also collected measures of well-being during the first pandemic year in a small group of 26 children (10♀/16♂; average age=10.69±2.52y/range 7-17y). They have previously taken part in a cross-sectional neuroimaging study together with their mothers (N=21, part of the sample reported in the manuscript) who agreed to be re-contacted and were invited to participate in the online follow-up assessments. All children had average intelligence: ≥75 in the German version of the Wechsler Intelligence Scale for Children (Daseking et al., 2007)). Children's retention rate per time point is reported in **Supplementary Table 4.1.1.**

Supplementary Table 4.1.1 Children's participation in the online survey and retention rate at each time point across the three assessment waves. Percentages are calculated based on 26 children taking part in the online study.

Timepoint		**Children**	**Children %**
W1	T0	38	Baseline
W2	T1	20	76.92%
	T2	25	96.15%
	T3	24	92.31%
	T4	23	88.46%
	T_E	24	92.31%
	T5	15	57.69%
	T6	23	88.46%
W3	T7	20	76.92%

4.2. Behavioral testing

Behavioral and emotional problems were assessed through the Strengths and Difficulties Questionnaire (SDQ; (Goodman, 1997), filled out by the mother at the assessment time points T2 to T6 (part of W2) and at the end of the first pandemic year (W3).

Additionally, potential associations of brain structure and later psychological well-being are tested in a small group of 26 children. Based on prior evidence (de Quervain *et al.*, 2020; de Quervain, 2020; Borbás *et al.*, 2021) we expect that the children will report heightened, but varying, levels emotional and behavioral problems across the first pandemic year.

4.3. Structural MRI

Structural T1-weighted MPRAGE images were available for the children as well and extracted data for the relevant brain structures and morphological features is provided in Supplementary Table 4.3.1. The data underwent the same procedures as in the adults' group. Further details can be obtained from the manuscript. Extra caution was paid during the quality assessment of the children's structural data, since the quality in paediatric samples has been suggested to be particularly affected by motion artefacts during the data acquisition. Each brain volume was expected slice by slice in axial, sagittal and coronal view by PD. Data quality allowed all participants to be included in the analyses.

Subject	Cortical thickness of the right dorsolateral prefrontal cortex
1	2.94
2	2.91
3	2.71
4	2.81
5	2.83
6	3.00
7	2.93
8	2.94
9	2.89
10	2.81
11	3.00
12	2.93
13	2.71
14	2.63
15	2.88
16	2.82
17	3.10
18	2.90
19	2.74
20	2.97
21	2.69
22	2.61
23	2.94
24	2.82
25	2.87
26	2.93

Supplementary Table 4.3.1 Extracted values of cortical thickness for right dorsolateral prefrontal cortex in children.

4.4. Data analyses

Behavioral data analyses of the children's data followed the same procedure as described for the adults' sample in the manuscript. Missing values were replaced using predictive mean matching as implemented in the Multivariate Imputation by Chained Equations package in R (MICE; (Buuren and Groothuis-Oudshoorn, 2010)). Comparisons of the scores indicating emotional and behavioral problems in the children during W2 and W3 were conducted using one-way repeated measures analysis of covariance (ANCOVA). Children surpassing clinically relevant cut-off scores (>13 in SDQ_{total}; (Mind, 2016)) are reported and compared using chi-square tests. Variation over time was tested through polynomial mixed-effect models.

4.5. Results

Variation in emotional and behavioral problems were tested. None of the scores revealed significant differences between children's well-being at W2 and W3, as reported in **Supplementary Table 4.5.1.**

Supplementary Table 4.5.1 Group characteristics and comparisons between the second (W2) and third (W3) assessment waves in children.

CHILDREN (N=26; 10 girls; mean age: 10.69 ± 2.52 y)

	W2	M ± SD		**W3**	M ± SD	*F*(1,23)	η2
Time since first testing	in months	18.76 ± 7.03	**Time since first testing**	in months	27.76 ± 7.03		
SDQ	externalizing	4.33 ± 2.57	**SDQ**	externalizing	3.88 ± 2.67	1.530	0.008
	internalizing	2.77 ± 2.28		internalizing	2.65 ± 2.33	0.122	0.001
	total	7.10 ± 4.21		total	6.54 ± 4.38	1.280	0.005

Emotional and behavioral problem scores reflected that 11.54% of all children reached heightened scores at W2 and 3.85% at W3, which did not differ significantly.

Changes in the emotional and behavioral problems in children over time were best characterized by a cubic model. Emotional and behavioral problems were increasing between T2 and T3 then decreased significantly during W2 and were elevated again at W3 (β_{linear}=0.14,$\beta_{quadratic}$=-0.02,β_{cubic}=0.0005). Details can be obtained from **Supplementary Table 4.5.2.**

Supplementary Table 4.5.2 Mixed models estimating the effect of time after restrictions have been introduced on children's behavioral and emotional problems. SE standard error, CI confidence interval, N (number of participants)/(number of observations). p-values were estimated by employing Satterthwaite approximation, significant effects are indicated in bold.

	Estimates	SE	CI (95%)	p
Intercept	1.79	0.21	1.38-2.20	**<0.001**
Duration linear	0.14	0.07	-0.001 – 0.29	0.055
Duration quadratic	-0.02	0.01	-0.04 - -0.01	**0.006**
Duration cubic	0.0005	0.0001	0.0002 – 0.001	**0.003**
N subjects/ observations	26/156			

The associations between rlPFC$_{CT}$ and W2/W3 mental well-being established in adults is not further reported for the subgroup of children, since the group size is too small. Data is nevertheless provided in order to for example allow possible future pooled analyses.

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