Integrative analyses of the brain networks underwriting everyday life social cognition

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1. Summary of the research plan

Theory of mind (ToM) is our capacity to infer someone else's emotions, beliefs, thoughts, and intentions, and is critical for efficiently navigating the social world. The understanding of the functional neuroanatomy of the ToM brain networks remains limited and controversial. While ToM deficits represent a hallmark of psychiatric conditions such as autism or schizophrenia, they have been largely neglected in neurological patients with acquired brain injury (ABI), such as stroke or traumatic brain injury. According to recent studies, ToM deficits occur in up to a third of ABI patients and have a substantial detrimental impact on everyday life.

The current clinical and scientific assessments of ToM are mainly stories, cartoons or still images, and lack the dynamics and complexity of real-life social situations, and therefore ecological validity. Following a thorough analysis of the literature, we have identified the Movie for the Assessment of Social Cognition (MASC) as one of the most ecological ToM assessment tools. This video-based task portraying naturalistic interactions within a group of peers was initially developed for autistic populations. Our previous study demonstrated the validity of the MASC in detecting everyday-relevant ToM deficits in ABI patients.

In the present proposal, our primary objective is to provide the first description of the eloquent (necessary) brain network components as well as causal and directed connectivity underwriting everyday-relevant ToM. To this end, Study 1 will entail Voxel-Based Lesion-Symptom Mapping (VLSM) and integrative disconnectome mapping across local lesion patterns, functional and structural connectivity in 180 ABI patients to assess the neuroanatomical underwritings of MASC performance. Study 2 will employ previously developed integrative analyses of structural and effective brain connectivity on MRI data in 36 healthy adults to explore the network for everyday-relevant ToM, and the relationships between whole-network level connectivity and behavior. We will also assess whether the affective (inferring emotional states) and cognitive (inferring thoughts, beliefs and intentions) components of everyday-relevant ToM are dissociated at the behavioral and neural levels.

This project will be the first to combine cutting-edge multimodal lesion mapping and connectivity analyses to uncover the functional neuroanatomy of the networks subserving everyday-life ToM. Concurrent evidence on the relationships between behavior and connectivity from neuroimaging and lesion mapping data is of utmost importance for understanding structure-function relationships in the brain. The outcomes will contribute to a better conceptualization of the brain networks underwriting ToM, and pave the way for better assessment and neurorehabilitation of deficits in social cognition.

2. Research plan

2.1 Current state of research in the field

2.1.1 Introduction: Theory of Mind in acquired brain injury

Social cognition, the inference of emotions, intentions or beliefs of others is fundamental for successful everyday life [1–4]. Day-to-day social cognition relies on the interpretation of multimodal, socially relevant signals such as face expressions [5–8], verbal content [9], but also voice prosody [10,11] and body language [12–15]. According to current psychological models of social cognition [16–18], affective and cognitive Theory of Mind (ToM) represent crucial processes for understanding the mental states of others. Affective ToM describes the inference of emotional mental states, whereas cognitive ToM represents the inference of cognitive mental states, such as thoughts, beliefs or intentions [19,20].

While ToM deficits are hallmarks of psychiatric conditions such as autism or schizophrenia [21,22], social cognition and ToM remain insufficiently considered in neurological patients with acquired brain injury (ABI), such as stroke or traumatic brain injury (TBI). This is surprising given the importance of social skills for everyday life [23–26], and the frequent affection of key ToM brain network components in ABI, such as the medial prefrontal and lateral parieto-temporal cortices [27,28]. Only recently available data suggest that about 34 % of ABI patients may suffer from ToM deficits [28–30]. Of note, this number matches the prevalence of executive cognitive deficits in stroke patients that, as opposed to social cognition, are recognized as a major issue in neuropsychology and neurorehabilitation [31].

Left undiagnosed and untreated, ToM deficits alter the patients' social behavior and everyday personal and professional interactions, affecting their well-being, and ultimately leading to social isolation [32–37]. Clinical providers of care for ABI patients also report a high prevalence of socio-cognitive impairments, and a significant but unmet need for their assessment and neurorehabilitation [38].

The lack of sound neuropsychological ToM assessments has played a substantial role in this inadequacy in ABI care [32,39,40]. Most of the currently available methods have been developed for the evaluation of ToM in psychiatric populations and may insufficiently fine-grained to target the constraints that ABI imposes on socio-cognitive abilities [39,40]. Furthermore, most ToM assessments lack ecological validity (verisimilitude and relevance for everyday life situations; [41]). In particular, the employed short stories, cartoons or still images often fall short in terms of the dynamics, speed, complexity and multimodality of daily-life social interactions [14,42–44]. Limited ecological validity and sensitivity might also explain why currently used, objective ToM measures are poor predictors of subjective measures of everyday life social cognition and functioning [45–48]. The present proposal will promote the assessment of ToM with everyday-relevant methods in ABI patients, ultimately leading to improved neurorehabilitation and care.

Lesion and imaging data indicate that the temporo-parietal junction (TPJ), superior temporal sulcus (STS), precuneus and temporal pole represent the predominant posterior brain regions involved in ToM [44,49–53]. More rostrally, the dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex

(dmPFC) are considered to primarily contribute to cognitive ToM [52,54–56], whereas some data have suggested specificity of the ventromedial prefrontal cortex (vmPFC) and inferior frontal gyrus (IFG) for affective ToM [20,57–61]. Recent findings also implicate the cerebellum in social cognition and ToM [62–68]. However, the functional neuroanatomy of ToM remains partly controversial and a matter of ongoing debate [54,69]. In particular, there is still an absence of studies assessing the dependence between ToM performance and connectivity within the underlying networks in healthy participants, and only limited evidence on the eloquence (i.e., necessity for intact function) of brain regions and connections for ToM in patients with brain damage. The present proposal intends to bridge this gap using a combination of cutting-edge multimodal connectivity analyses in neurotypical adults and lesion-symptom and disconnectome mapping in ABI patients, in order to contribute to improved conceptualization of the functional neuroanatomy of everyday-relevant ToM.

2.1.2 Everyday-relevant assessment of ToM

According to our recent in-depth analysis, the Movie for the Assessment of Social Cognition (MASC) [42] represents one of the currently most sensitive and ecological ToM evaluation methods [39]. The only comparable approach is the Awareness of Social Inference Test (TASIT; with video vignettes depicting dyadic social interactions; [70]) that has recently been translated to German and validated in healthy German-speaking adults [71]. So far, only the MASC is available in several languages including German, English, Spanish and French, along with a recently available French normative data set [72].

The MASC is a 15-minutes scripted movie consisting of continuous scenes featuring four actors portraying friends (two females and two males) meeting for dinner on a Saturday night. The storyline closely reflects typical everyday adult interactions and the participants have to infer each protagonist's stable traits and transitory affective (emotions) and cognitive (thoughts, intentions) mental states based on overt and covert behavior of the actors. Each of the scenes is followed by one or several questions about the mental states of the characters ("What is Michael feeling?", "What is Betty thinking?", "What is Michael trying to do?"). The answer format (*Figure 1*) contains a correct answer (appropriate inference), and three incorrect answers: a hypermentalization (the interpretation is excessive), a hypomentalization (the interpretation is insufficient, or incomplete), and an absent mentalization (the interpretation is not a mental state). Control questions refer to environmental or physical features.

Originally developed for autistic individuals, a recent study showed MASC performance deficits in TBI patients when compared to healthy controls, and an association between these deficits and behavioral executive impairment [33]. Some neuropsychological clinics in Switzerland including our Unit of Neuropsychology at the Department of Neuropsychology and Neurorehabilitation at the Centre Hospitalier Universitaire Vaudois (CHUV) have already used the MASC for the assessment of ToM in ABI patients. However, the validity of the MASC in neurological conditions has remained unclear. Recently, we have conducted a neuropsychological validation study in ABI patients [73].

***Figure 1*. MASC sample question. *Left*: screen capture of video clip. *Right*: associated question with answer format (hypermentalization, correct mentalization, absence of mentalization, hypomentalization; *colored frames and answer categories added for illustrative purposes*).**

The intermediate outcomes indicate promising discriminant validity, convergent validity, internal consistency, sensitivity-specificity, and test-retest reliability of the MASC in people with socio-cognitive complaints due to ABI. Patients (N = 15) score significantly lower than controls (N = 11) matched for age, sex, and socio-cultural status (W = 19.5, p = 0.00113; *Figure 2A*). Furthermore, subjective self-reported deficits in everyday life social cognition on the Observable Social Cognition Rating Scale (OSCARS) questionnaire [69] exhibit a significant negative correlation with MASC performance (ρ = -0.53; p = 0.006). Confirming previous studies in autistic individuals [42] and borderline personality disorder patients [74], among several social cognition assessments including the Reading the Mind in the Eyes test (RMET; [75]), the MASC is the most accurate indicator of socio-cognitive deficits (*Figure 2B*). These findings underline the value of the MASC as a highly sensitive, specific and ecological neuropsychological method for ToM assessment in ABI.

To the best of our knowledge, the only investigation of the neural correlates of MASC performance was a functional magnetic resonance (fMRI) activation study with a shortened version in 19 healthy participants [76]. The reported activations were located in the precuneus, TPJ/STS, temporal pole, dmPFC and IFG – regions generally implicated in ToM in other fMRI and lesion mapping studies. However, the relationships between performance on this reliable proxy of everyday social cognition and brain anatomy remain unclear.

2.1.3 The neural correlates of ToM

Convergent evidence from lesion studies and neuroimaging is fundamental for advancing models of the anatomy and compensatory potential of the brain [62–64,77–79]. Linking brain activation and connectivity derived from task-based functional neuroimaging to behavior can afford highly useful insights on functional neuroanatomy [56,61,80,81], but functional neuroimaging evidence is not sufficient to determine eloquence, i.e. whether a certain function depends on the integrity of a specific network component. On the other hand, lesion mapping approaches aim at establishing the relationship between injured brain tissue and behavioral deficits. While traditional lesion-symptom mapping [82] can

be regarded as a localizationist approach, novel methods such as disconnectome mapping assess the effects of lesions on networks. Disconnectome mapping enables more neurobiologically plausible conclusions on the causes of behavioral impairment, not only considering focal damage, but also altered connectivity of the lesioned brain areas with other parts of the brain [83,84]. In turn, these local and network lesion mapping approaches fall short of revealing the precise pattern of brain network dynamics, such as afforded by effective connectivity analyses in neuroimaging.

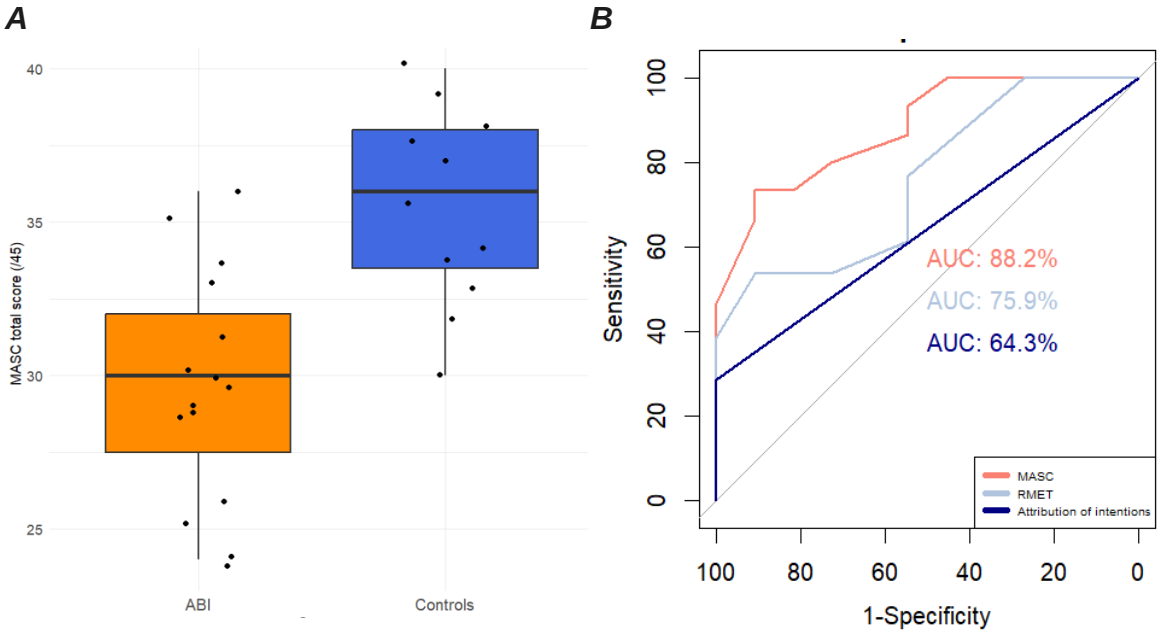

***Figure 2*. (A) Patients with ABI (in orange) exhibit significantly lower performance on the MASC than healthy matched controls (blue). The boxplots' central lines indicate the median. Whiskers indicate the interquartile ranges. (B) The receiver operating characteristic curves show that the MASC (red curve) is a significantly more accurate predictor of socio-cognitive deficits due to ABI than the RMET (light blue curve) and the attribution of intentions comic strip task (dark blue curve). AUC: area under the curve.**

Effective connectivity refers to the causal, asymmetric and context-dependent influence that neural populations exert over each other [85,86]. Effective connectivity generally allows a more detailed analysis of functional dynamics and crosstalk than functional connectivity [87,88]. The latter refers to the correlations in activity of remote brain regions [89,90], resulting from the causal, effective interactions between them. Importantly, in contrast to functional connectivity, effective connectivity analyses such as dynamic causal modelling (DCM) can capture the direction of communication [86], with asymmetry being considered a potentially fundamental principle of functional neuroanatomy [91]. In addition, our recent research indicates that including measures of white-matter, structural brain connectivity affords more veridical representation of brain communication in DCM [80,92,93]. In the present proposal, combining integrative lesion mapping approaches with multimodal connectivity analyses, we intend to provide initial convergent evidence on the cerebro-cerebellar networks underwriting everyday-relevant ToM.

2.1.3.1 ToM lesion mapping and activation studies

These analyses will contribute to filling the significant gaps between imaging, stimulation and lesion data on ToM outlined below. Neuroimaging has revealed widespread brain activation during ToM processing, mainly in the superior lateral and anterior temporal lobe, precuneus, medial and lateral prefrontal cortex and the cerebellum. However, there are significant discrepancies in the availability and coherence of evidence on the different parts of the social brain.

Consistent brain imaging data link activation in the STS/TPJ, precuneus and temporal pole to inferences on the affective and cognitive states of others [44,49–53]. However, only one voxel-based lesion-symptom (VLSM) study in tumor patients reported that parieto-temporal areas may be eloquent for ToM processing. The outcomes suggested specific involvement of the right superior parietal cortex in cognitive ToM, and the right antero-medial temporal cortex in affective ToM [94], converging with previous fMRI data on preferential activation of the temporal pole for affective versus cognitive ToM [51]. Specific involvement of the superior parietal cortex in cognitive ToM was also recently demonstrated in patients with fronto-temporal dementia [95].

For the prefrontal cortex, more lesion data are available, however, with somewhat limited consistency. Damage to the IFG has been frequently reported to result in deficient ToM. In 93 patients after low-grade glioma neurosurgery, integrity of the right IFG and arcuate fascicle predicted RMET performance [60], most closely related to affective ToM, the inference of the affective states of others [43,96]. Upon extension of the sample to 122 patients, only damage to the right arcuate fascicle appeared to exhibit a significant effect on RMET performance [97]. This underscores the relevance of a sufficient sample size and disconnectome analyses such as proposed in the present project. RMET scores were also associated to stroke lesions in the right posterior frontal gyrus, the insula, as well as the right inferior longitudinal fasciculus, right frontal aslant tract, fornix, and anterior commissure [28]. In TBI patients, RMET performance depended on the integrity of the left IFG [59]. Interestingly, a DCM study assessing effective connectivity during ToM indicated the bilateral IFG may represent a gateway for information flow to the medial PFC, precuneus and STS/TPJ [98]. Until now, to the best of our knowledge, these are the only convergent lesion-symptom and effective connectivity findings in the ToM literature.

The medial PFC is considered another important hub of the ToM network. An fMRI study in healthy participants implicated the dmPFC in developing and updating cognitive ToM models predicting the behavior of others [56]. Seminal lesion-symptom mapping studies in ABI patients specifically located affective ToM to the vmPFC, however with only limited sample sizes of 11 and 13 ABI patients, respectively [20,57]. Using fMRI during the interpretation of written social scenarios in healthy participants, preferential involvement of the medial orbitofrontal cortex was reported for affective versus cognitive ToM [58]. When viewing photographs of ambiguous social interactions, activation levels of the vmPFC predicted the inference of the affective states of the protagonists [61]. On the other hand, fMRI studies using cartoon tasks on social interactions and sequences showed common activations for cognitive and affective ToM in several brain areas including the vmPFC and dmPFC [51,99]. Moreover, VLSM in TBI patients indicated involvement of the left vmPFC in detecting social faux pas, requiring

both affective and cognitive inferences [100]. Specific activation of the dmPFC was shown for affective as opposed to cognitive inferences from social short stories [101]. During performance of a cartoon task, affective inferences were mapped to the dmPFC and IFG, and cognitive inferences to the precuneus and STS [102]. A meta-analysis of over 105 studies suggested predominantly overlapping or adjacent activations for affective and cognitive ToM across the social brain, but specific involvement of the IFG in affective ToM [103].

The dlPFC has been primarily associated with inferences on the cognitive mental states of others. Repetitive transcranial magnetic stimulation (rTMS) over the dlPFC in typically developing adult males resulted in impaired performance on cognitive, but not affective ToM [54]. Performance on the strange stories task (cognitive ToM; [9]) was impaired in TBI patients with right dlPFC damage and disconnection of the left inferior longitudinal and right superior longitudinal fascicles [27]. Deficits on the same task were reported in TBI patients with lesions to the left lateral cerebellum, and with disconnection of the left thalamic projection and left fronto-striatal fasciculus [104]. In low-grade glioma patients, post-operative performance on a cognitive ToM comic strip task depended on the right IFG, middle frontal gyrus, supplementary motor area and cingulum fiber bundle [60]. Overall, the IFG, medial PFC and dlPFC are among the most commonly prefrontal areas implicated in lesion mapping and activation studies on ToM. Partly controversial data suggest the vmPFC, IFG and potentially the dmPFC may contribute predominantly to affective ToM, and the dlPFC to cognitive ToM.

2.1.3.2 Lesion and disconnectome mapping of everyday-relevant ToM (Study 1)

Taken together, the currently available lesion-symptom, brain imaging and brain stimulation data indicate a widely distributed ToM network mainly involving the TPJ, STS, precuneus, anterior portions of the temporal lobe, IFG, vmPFC, dmPFC, dlPFC, the left lateral cerebellum, and white-matter pathways connecting them. However, the data are heterogeneous and there is a lack of evidence on the eloquence of these network components for everyday-relevant ToM outside of paper-and-pencil tasks or short stories with limited ecological validity.

Among the VLSM and disconnectome data reviewed above, to the best of our knowledge, only seven studies addressed ToM in ABI patients, with heterogeneous test materials evaluating different aspects of social cognition. Four of the studies were conducted in a cohort of military veterans with chronic penetrating TBI, with sample sizes ranging from 106 to 193 patients per study. Crucially, these studies in penetrating TBI were performed on computed tomography (CT) exclusively, due to MRI contraindications. This is a major limitation, given the low resolution of CT in terms of the extent and number of brain lesions, as compared to MRI [105]. Furthermore, in the veteran studies, the well documented detrimental effects of post-traumatic stress disorder on social cognition [106] do not seem to have been taken into account, representing a significant caveat when interpreting the available evidence on relationships between brain anatomy and ToM. Only one lesion-symptom study with a moderate sample size (N = 64) is available in stroke patients, using both CT and MRI, and insufficient coverage of the prefrontal cortex, as expected for stroke lesions most often affecting the medial cerebral artery territory [28]. On the other hand, affection of the regions adjacent to the major ToM network hubs

TPJ and STS was substantially limited in the TBI [27] and tumor studies [60,97] discussed above. The etiology and age of brain damage may also result in divergent functional outcomes despite similar lesion topography [107,108].

In Study 1 of the present proposal, we intend to provide initial VLSM and disconnectome mapping data on everyday-relevant ToM in 180 patients with TBI or stroke. Inclusion of both stroke and TBI patients will improve the coverage of prefrontal, parieto-temporal and cerebellar regions. Furthermore, the mapping will be performed exclusively on MRI data acquired at the time of ToM assessment. Using these high-quality and generalizable lesion mapping data, we aim at clarifying which network components are eloquent for everyday life ToM.

2.1.3.3 Effective connectivity in the ToM network

Analyzing the behavioral outputs of brain activity and connectivity recorded by brain imaging represents a useful complement to VLSM and disconnectome mapping [62–64,77]. Despite the ongoing paradigm shift in neuroscience towards network-level concepts of brain function [109,110] including social cognition [111], the vast majority of current task-related fMRI studies of ToM in healthy participants including the only published study on the MASC [76] still focus on local activation patterns that may not be sufficient for adequately explaining social cognition and behavior [112].

Over the past few years, assessment of directed effective connectivity has emerged in the domain of ToM. In addition to the previously discussed DCM findings on a potential gatekepper role of the IFG in the ToM network [98] converging with lesion-symptom mapping data [59,60], a study showed that inferring the indirect meaning of spoken information enhanced the effective connectivity from the IFG to medial PFC [113]. Conversely, during ToM based on pictures of emotional face expressions, feedforward effective connections were found from the STS to the IFG and inferior parietal lobule, rather suggesting a gatekeeper role of the STS [114]. Bidirectional effective connectivity between the TPJ and anterior cingulate cortex was found during socially relevant attention [115]. Interestingly, schizophrenia patients show sparser input from the TPJ to the dmPFC, related to aberrant interpersonal behavior [116].

In an experimental paradigm more closely resembling the naturalistic MASC in the present proposal, when interpreting emotional video vignettes featuring the participants' romantic partners, DCM analyses indicated a coordinator role for the precuneus, and specific engagement of the TPJ when reflecting on the experience of others [117]. A series of DCM studies also described reciprocal effective connectivity between the posterior lateral cerebellum and TPJ across various ToM contexts [65–68]. In addition, when processing trait-implying social action sequences, the medial PFC exhibited effective connectivity with the cerebellum and TPJ [67].

Overall, the rather heterogenous effective connectivity patterns and implications of specific regions and connections in the ToM network point to a modular organization of the ToM network, with parallel and interacting hierarchical bidirectional information flow between the parieto-temporal and prefrontal regions, e.g. the TPJ/STS, IFG and medial PFC, similar to the architecture of the network for body

language reading [80]. The use of experimental paradigms with varying content and cognitive demands appears to have contributed to highlighting only the task-specific subcomponents and potential gatekeepers of the network. This limitation will be overcome in the present proposal, using the multimodal and naturalistic MASC that has been shown to elicit widespread activation of the ToM network [76]. Importantly, the present proposal will also contribute to clarifying the relationship between connectivity in the ToM network and everyday-relevant ToM performance.

2.1.3.4 Integrative connectivity analyses of the brain networks underwriting ToM (Study 2)

Our understanding of brain function based on network analyses depends critically on the optimal use of the breadth of the multimodal information afforded by neuroimaging. Long-range communication and dynamics in the brain rely on white-matter pathways, calling for combined analyses of structural and effective brain connectivity [118]. Both effective and structural connectivity analyses have contributed to better conceptualizing the distributed networks subserving more basic social cognition processes, such as the recognition of face or gaze expressions, reading of body language, perception of social interactions, and everyday life sensitivity to social information [80,119–124]. Some of these studies provided convergent evidence from structural and effective connectivity, but integrative analyses remained scarce. Formally integrative analyses of effective and structural connectivity are complex, as their relationship is not straightforward due to inherently different biophysical underpinnings [89,92,93,125].

In order to overcome this methodological issue, we have previously developed structurally informed Parametric Empirical Bayes (si-PEB), an efficient automated approach for integrating effective and structural connectivity [80,93]. Our analyses demonstrated that inclusion of measures of structural white-matter connectivity derived from diffusion MRI in DCM analyses of effective connectivity in fMRI data affords significant information benefits [92,93]. Along with an innovative canonical variate approach for predicting behavior from whole-network connection strengths, si-PEB yielded novel insights on the functional organization of the cerebro-cerebellar network for body language reading [80].

In Study 2 of the present proposal, we will capitalize on these methodological advances using task-related functional MRI and diffusion MRI data to assess the multimodal cerebro-cerebellar connectivity underlying naturalistic ToM including network-level associations between connectivity and behavior in 36 healthy participants. Study 2 will set the stage for a better understanding of the neural dynamics underwriting everyday life social cognition. The outcomes of Study 2 will be complementary to the VLSM and disconnectome mapping approaches in Study 1, providing convergent conclusions on the functional neuroanatomy of the brain networks for everyday-relevant ToM.

2.1.3.5 Affective and cognitive components of everyday life ToM

The inferences about affective and cognitive states are generally conceptualized as two separate subcomponents of ToM [16,17]. At the neuroanatomical level, lesion-symptom mapping, brain stimulation and imaging findings suggest predominant implication of the IFG, vmPFC and anterior temporal lobe in affective ToM [59,60,98], whereas the dlPFC and superior parietal cortex appear to

primarily engage in cognitive ToM [27,54,94,95]. As discussed above, the evidence is partly controversial, and several meta-analyses suggest shared or overlapping involvement of most of the aforementioned brain regions in both processes [44,103,126]. Disentangling the contributions of inferences about the affective and cognitive states of others to everyday life ToM and their neural underpinnings would be essential for designing specific efficacious approaches for the neurorehabilitation of social cognition [127].

Previous theoretical reasoning suggested more naturalistic ToM contexts may elicit fMRI activation across both components through network integration [44,128]. However, unless most of the available ToM assessments, the MASC allows parsing out affective and cognitive ToM through specific questions inducing one or the other context within the same stimulus material [42]. A study using the MASC revealed a specific affective ToM deficit but preserved cognitive ToM in alcohol-dependent individuals [129]. Secondary analyses in the present proposal will assess whether neurotypical participants and ABI patients exhibit behavioral and neural differences between the affective and cognitive contexts of the MASC. In Study 1, we will include separate lesion-symptom mapping analyses on affective and cognitive ToM performance. In Study 2, the use of DCM and a priori contextualization of each trial into affective, cognitive or non-social using an adapted version of the MASC (*Figure 3*) will allow assessing potential context-dependent enhancement or silencing of specific effective connections in the network, even in the absence of differential network architecture. According to previous findings, we expect the integrity and connectivity of the anterior temporal cortex, IFG and medial PFC to be important for affective inferences, and of the dlPFC and superior parietal cortices for cognitive inferences. The outcomes will contribute to establishing a consensus on the mechanisms underlying the everyday life inferences on the affective and cognitive states of others.

2.2 Current state of own research

Social cognition both in clinical and neurotypical populations has been a key element of the applicant's research activity over the past 18 years, and the implementation of everyday-relevant ToM assessments in neuropsychology and neurorehabilitation is among the principal current clinical and academic aims of the applicant. Following an in-depth analysis of the available assessment methods pointing to the MASC as one of the most sensitive and ecological approaches [39], a validation study was conducted on the utility of the MASC as an everyday-relevant neuropsychological assessment of ToM in patients with ABI at the Unit of neuropsychology led by the applicant at the Department of neuropsychology and neurorehabilitation at the CHUV. The encouraging outcomes of this study have led to the development of the present proposal on the neurobiological foundations of everyday ToM. In a similar vein, we recently published a review focusing on neurorehabilitation of social cognition in immersive virtual reality, concluding that these programs were promising in terms of transfer of the learned socio-cognitive abilities to real life, particularly due to their ecological validity [40].

The applicant has a strong background and expertise in neuropsychological and brain imaging research on social cognition. Previous work examined the capacity to perceive emotions from body language and associated gender differences, as well as the underlying brain networks [81,130], revealing that the

limbic system also contributes to the recognition of emotionally neutral signals. Convergent lesion-symptom mapping and connectivity analyses have elucidated the normal and pathological structure and function, as well as the compensatory potential of social brain networks in patients with cerebellar damage and fronto-temporal dementia [62–64,131]. In particular, the applicant provided pioneering evidence on involvement of the left lateral cerebellum in body language reading in neurosurgical patients with cerebellar tumors [62]. In healthy participants, effective and structural connectivity studies afforded the first evidence for a direct reciprocal connection between the left lateral cerebellum and the right STS, a major hub of the brain networks for social cognition [63,64]. This work has led to influential concept and international expert consensus papers on the involvement of the cerebellum in social cognition [132–135]. As mentioned above, the applicant also developed si-PEB, a method for the integrative assessment of structural and effective connectivity [93]. Si-PEB has already revealed several key principles of the organization of social cerebro-cerebellar networks underwriting body language reading [80]. The applicant also introduced a method for the prediction of behavior based on whole-network instead of region-to-region measures of connectivity [80]. Study 2 will capitalize on both approaches.

During the Covid-19 pandemic, the applicant contributed to a seminal analysis of the effect of face-covering masks on face perception and social cognition [136]. Finally, recently published work investigated the validity and potential confounds of the widely used RMET for the assessment of ToM in healthy and clinical populations [43]. Overall, this previous work laid ground for the hypotheses and methods outlined in the present proposal.

2.3 Detailed research plan

2.3.1 Study 1: Lesion and disconnectome mapping of everyday-relevant ToM

2.3.1.1 Principal objective and hypothesis

We intend to study the eloquence of areas and pathways for intact performance on an ecological and multimodal ToM task using integrative lesion-symptom, as well as functional and structural disconnectome mapping in 180 ABI patients. Based on previous data, we hypothesize that MASC performance will depend on integrity of the IFG, dlPFC, medial PFC, superior parietal cortices and the temporal pole. The disconnectome analysis will specifically assess the role of connections between these areas and the STS/TPJ, precuneus and cerebellum in everyday-relevant ToM performance.

2.3.1.2 Participants

180 neurological outpatients (age ≥ 18 years) at > 3 months after onset of supra- or infratentorial lesions due to ischemic or hemorrhagic stroke or TBI will be enrolled in Study 1. The time period of 3 months after lesion onset and the focus on outpatients will contribute to the clinical relevance of the findings in two ways: (1) deficits towards the end of the period of maximal brain plasticity and recovery [137] will be more likely to persist and interfere with everyday life and prognosis; (2) outpatients and their next-of-kin will have had sufficient exposure to potential changes in everyday social cognition and behavior,

increasing the relevance of reported deficits and their association to MASC performance. Exclusion criteria will be contraindication for brain MRI, a diagnosis of autism, schizophrenia or post-traumatic stress disorder, a diagnosis of severe substance abuse, and the inability to undergo the MASC or other neuropsychological testing (e.g. insufficient French skills, severe visual impairment, presence of moderate or severe disorders of oral and written comprehension at the Test Informatisé de Compréhension Syntaxique en français (TICS-f-12; [138])). The study protocol will be submitted for approval to the Cantonal Ethics Committee, and informed written consent will be obtained.

The patients will be recruited over 36 months from the specialized cognitive and behavioral neurology and neurorehabilitation consultation of the applicant, or the neuropsychological assessment or rehabilitation consultations at the Unit of neuropsychology led by the applicant at the Department of neuropsychology and neurorehabilitation of the CHUV in Lausanne. Feasibility analyses indicate 5-7 eligible outpatients per month, confirming feasibility of completing enrolment within the planned time window. Dedicated structural MRI will be performed if the most recent clinical MRI is > 28 days before or after the ToM assessment, in order to ensure optimal accuracy with respect to potential evolution of the lesion pattern since onset.

Given the absence of formal power analyses for VLSM, the sample size was defined according to current recommendations and simulations [108,139–141], with an expected prevalence of 30 % of ToM deficits in ABI patients, based on recent data [28–30]. The sample size of 180 patients corresponds to the upper range of currently available VLSM and DSM studies on ToM, but also other cognitive and behavioral domains [142]. This will allow drawing more reliable conclusions and including a greater variety of lesion topography patterns.

2.3.1.3 Behavioral measures

A dedicated social cognition test battery will be administered to each patient by a trained neuropsychologist (Dr P. D'Honincthun), assisted by the doctoral student trained and supervised by the neuropsychologist. The social cognition battery will consist of the MASC, the Geneva Emotion Recognition Task-short (GERT-S; a dynamic ecological emotion recognition task; [143]) and the International Affective Picture System (IAPS; a measure of emotional contagion; [144]). Furthermore, we will assess subjective measures of attribution bias (Ambiguous Intentions Hostility Questionnaire; AIHQ; [145]) and social functioning: the OSCARS [69] and the Interpersonal Reactivity Index (IRI; [146]) in their self-/ and proxy-administered versions. The patient will be seated in a quiet room, and the tests will be administered on paper material and a notebook PC.

Potential factors that may influence ToM performance will also be assessed and included in the analyses. For instance, depression and anxiety will be evaluated with the Hospital Anxiety and Depression Scale (HADS; [147]), as mood disorders and anxiety have been shown to skew social perception and ToM [148–150]. Verbal comprehension will be probed using the TICS-f [138]. We will also assess the relationships between ToM performance and executive function [69,151], as evaluated in the clinical neuropsychological assessment or, if unavailable, obtained during the experimental

session. This will include inhibition, flexibility (D-KEFS Stroop test; [152]; and Trail Making Test B; TMT-B; [153]), verbal working memory (word span; [154]) and processing speed (TMT-A; [153]).

2.3.1.4 Behavioral analyses

The primary behavioral analysis will rely on a regression model with MASC total scores as the dependent variable and scores for lower-level emotional processes (such as emotional contagion), mood and anxiety symptoms, attribution bias, verbal comprehension, executive functions, verbal working memory and processing speed as the independent variables to determine their individual contribution (adjusted R^2) to ToM performance on the MASC. Prior to entering the regression model, predictors will be tested for multicollinearity with correlations. Predictors with a correlation coefficient ≥ 0.60 will be summarized by a single variable in the regression model.

In secondary analyses, we will assess the relationship between MASC performance and everyday life social cognition, using a regression model with the MASC, GERT-S and IAPS as dependent variables and subjective measures of everyday life social cognition (OSCARS and IRI) as independent variables. We will also calculate the proportion of patients scoring below the cut-off [72] to provide a preliminary estimate of the prevalence of everyday-relevant ToM deficits in ABI patients, with a calculated precision of 6.69 % (with 30 % expected prevalence, 95 % CI, and 180 participants).

The behavioral data analysis will be performed by a trained researcher (doctoral student), together with and under the supervision of a neuropsychologist, the postdoctoral researcher and the principal investigator.

2.3.1.5 Voxel-based lesion-symptom mapping (VLSM)

The main feature and advantage of VLSM is that it reveals brain areas that are associated to a behavioral function on a voxel-by-voxel basis, without requiring predefined regions of interest. In a nutshell, for each voxel, a *t*-test is performed on the behavioral scores between the groups of patients with and without lesion to this voxel [82].

We will obtain T1-weighted, fluid attenuated inversion recovery (FLAIR) and susceptibility weighted imaging (SWI) MRI sequences either from the patients' records (if conducted ≤ 4 weeks around the administration of the social cognition battery) or from MRI recordings performed in the context of this study. Following state-of-the-art recommendations for ABI [142], lesions will be manually segmented on individual structural MRI images (T1-weighted, FLAIR and SWI images) using the Analyze biomedical imaging software system (www.mayoclinic.org; [155]). Two qualified team members (postdoctoral fellow and principal investigator/neurologist) will independently assess and correct the lesion masks. (Sub)acute-phase MRI will also be reviewed whenever available, and potential clusters of microbleeds in TBI patients will be noted and reported in the absence of a formally validated analysis method. Of note, recent evidence indicates an absence of relationship between presence and topography of microbleeds, diffuse axonal injury and cognitive performance or domain-specific impairments [156]. The manually corrected and validated lesion maps will then be normalized to the

Montreal Neurological Institute space (MNI152; http://www.bic.mni.mcgill.ca/). Subsequent VLSM analyses will be carried out by the doctoral student and the postdoctoral researcher, under the supervision of the principal investigator.

First, a lesion density map of all patients will be calculated. Second, following the procedure by Kimberg et al. [140], we will eliminate the influence of potential confounds related to executive deficits, mood disorder, anxiety or attribution bias by entering them in a regression model as predictors and MASC scores as the dependent variable. Only the residuals of this analysis will be kept as MASC corrected scores for subsequent VLSM and disconnectome mapping analyses. In the principal VLSM analysis, we will perform voxel-wise group comparisons on corrected MASC scores for overall ToM performance using the VLSM package version 2.60 (https://aphasialab.org/vlsm/) in Matlab R2017a (Mathworks, Natick, MA) [82,157]. Automated Anatomical Labeling (AAL; [158]) and Natbrainlab [159] atlases will be used to identify the brain regions and white matter tracts associated with significant voxels ($p < 0.05$). For each analysis, we will correct for multiple comparisons using permutation testing, a resampling procedure similar to bootstrapping but without replacement, particularly suited for large sample sizes [108,140,160].

A secondary analysis will assess whether and which lesioned brain areas may be specifically eloquent for affective or cognitive ToM. To this end, we will compute the difference between the corrected MASC subscores for affective and cognitive ToM, and enter this differential score in a VLSM to explore the neural correlates of a potential affective-cognitive "gap" in ToM performance [94].

2.3.1.6 Integrative lesion, structural and functional disconnectome symptom mapping

While VLSM is effective for the investigation of the relationship between apparent lesions and behavior, it does not perform optimally when white matter disconnections affect remote cortical functioning in otherwise intact areas [84]. Disconnectome mapping as implemented in the BCBtoolkit v4.0.0 [83] has become increasingly used to map the structural and functional disconnections caused by focal lesions. To generate a disconnectome for each patient, we will use our patients' lesion masks and the 3T diffusion-weighted and functional MRI datasets of 180 healthy adults from the Human Connectome Project (HCP; https://www.humanconnectome.org/; age range: 22-100+), randomly selected from individuals matching our patients' age, handedness and gender as closely as possible. We opted against the 7T Human Connectome database (participants' age range 22-35 years) to avoid potential confounding effects of the expected age differences between this cohort and the patients recruited in our study [161]. Disconnectome mapping will be performed by the doctoral student and the postdoctoral researcher, under the supervision of the principal investigator.

For structural disconnectomes, the patients' lesion masks in MNI space will be transformed to the native space of each HCP healthy participant's tractography data using affine and diffeomorphic deformations [162,163]. Once in the native space of controls, the lesion masks will serve as a seed for tractography. This will result in a binary visitation map (marking voxels crossed by at least one tract with a 1, and those not crossed by any tract with a 0) per lesion and healthy individual. The visitation maps will be

transformed back to the MNI space. By overlapping all the visitation maps, we will obtain a voxel-wise probability of white-matter disconnection for each lesion ranging from 0 to 100% [83].

For functional disconnectomes, we will use the same HCP healthy participants' resting-state functional connectivity data to estimate the average Pearson correlation between the time course of the brain region corresponding to the lesion and the rest of the brain [142]. Each patient's lesion transformed to native space will serve as a seed region of interest for a whole-brain resting-state functional connectivity analysis in each of the matched HCP controls. The resulting functional connectivity maps will be transformed in the MNI stereotaxic space to produce a functional disconnectome, with the value of each voxel indicating an average strength of correlation between −1 and +1 between the time course of the lesioned region and the rest of the brain.

The principal disconnectome mapping analysis will be performed according to a recently introduced, state-of-the-art integrative approach on the overall contribution of lesions, functional and structural disconnection to behavioral deficits [164]. This will help overcoming the heterogeneity of previous separate analyses, incorporating the major local and remote lesion-dependent influences on behavior into a single, comprehensive model. Using the FSL software package (http://www.fmrib.ox.ac.uk/fsl/, version 5.0), structural and functional disconnectome maps will be entered as dependent variables within a general linear model comparing patients with ToM deficits (MASC total scores < 1.5 SD of healthy controls) and without ToM deficits (MASC total scores ≥ 1.5 SD of healthy controls). Potential confounds related to executive deficits, mood disorder, anxiety or attribution bias will be entered as covariates. Permutation testing will be used to correct for family-wise errors. Statistically significant ($p < 0.05$) cortical areas, functional connections and white matter pathways will be compared and labeled with the Harvard-Oxford Atlas [165] and the atlas of human brain connections [166]. Taken together, this approach will provide an integrative view of the neuroanatomical foundations of everyday life ToM.

2.3.2 Study 2: Integrative effective and structural connectivity in the ToM networks

2.3.2.1 Principal objective and hypothesis

Using multimodal effective and structural connectivity measures, we will assess the architecture, causal and directed communication and behavior-connectivity relationships within the brain networks for everyday-relevant ToM in 36 healthy adults. Our principal objective is to delineate whole-network level relationships between structurally informed effective connectivity and ToM performance. Based on the previously discussed work, we hypothesize the ToM brain network to consist of hierarchically organized, interacting modules, with multiple reciprocal streams of information between the precuneus and STS/TPJ in the posterior part of the network, and the IFG, dlPFC and medial PFC in the rostral part of the network, including the temporal pole and superior parietal cortex as relays in some of the modules. We expect the cerebellum to exhibit reciprocal interactions with several of the above mentioned network nodes, in particular the STS/TPJ and medial PFC. The outcomes will contribute to a more fine-grained neurobiological model of ToM.

2.3.2.2 Participants

We will recruit 36 healthy participants (age ≥ 18 years; right-handed; 1:1 male-female ratio) with no history of neurological or psychiatric conditions, head injury or psychoactive treatment, as well as no MRI-specific contraindications such as cardiac pacemaker or metal implants. Left-handed people will not be included in this initial study since handedness may have an influence on the lateralization of social cognition [167]. The study protocol will be submitted for approval to the Cantonal Ethics Committee, and informed written consent will be obtained.

2.3.2.3 fMRI-adapted MASC

We will adapt the MASC for our fMRI experiment, with the aim to obtain three conditions with 15 items each: affective ToM, cognitive ToM, and a control condition (non-ToM) with similar attentional demands as the ToM questions. To this end, we will introduce an a priori contextualization (Emotions for affective ToM, Thoughts for cognitive ToM, Features for non-ToM; *Figure 3*) and replace nine ToM by non-ToM questions in a pseudo-randomized fashion (for a better estimation of the hemodynamic response function). The adapted task will feature the same audiovisual material as in the original MASC. The MASC will be presented in three blocks, each with five trials per condition.

The stimuli will be projected onto an MRI-compatible monitor viewed by the participants through a tilted mirror on the MRI head coil. The sound will be delivered by MRI-compatible headphones (Sensimetrics Model S14, USA), successfully used in previous fMRI studies on film viewing [168]. Each fMRI trial (*Figure 3*) will include the contextualization cue (1000ms), the MASC video clip (mean duration 20s), and a four-option multiple-choice question with a response timeframe (11s, based on our pilot testing in healthy participants). Participants will provide their answers using four buttons. The remaining time to answer will be indicated with a bar gauge on the upper part of the screen, and participants will be informed by an on-screen message once their answer is recorded. The next trial will start after the end of the response timeframe.

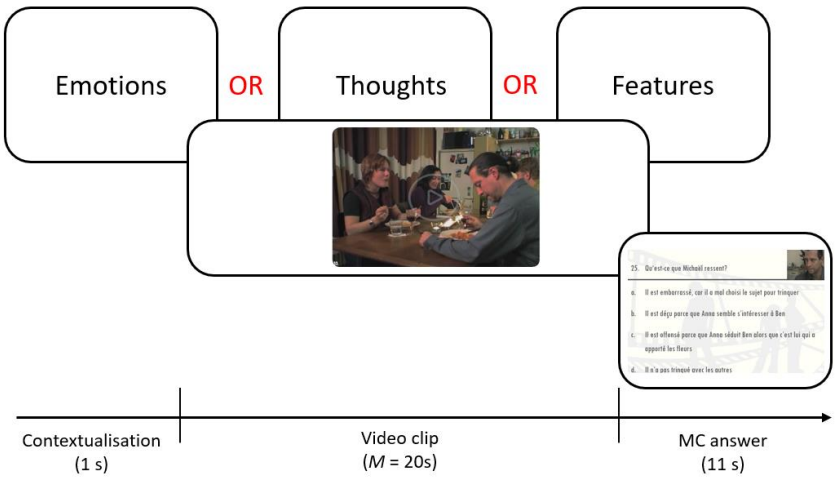

Figure 3. **fMRI task. A trial starts with a contextualization cue (emotions for affective ToM, thoughts for cognitive ToM, or features for non-ToM) indicating the type of question that will be asked after the video clip. The MASC video clip is then presented, followed by the multiple-choice question.**

2.3.2.4 MRI acquisition and processing

Structural, functional and diffusion MRI will be recorded using a 3T Magnetom Prisma MR scanner (Siemens Healthcare, Erlangen, Germany) at the MRI Platform, Department of Clinical Neuroscience, CHUV. For each participant, a T1-weighted magnetisation-prepared rapid gradient echo (MPRAGE) imaging dataset (176 sagittal slices, TR = 2300 ms, TE = 4.16 ms, TI = 900 ms, and voxel size = 1 × 1 × 1 mm^3) will be acquired as an anatomical reference. During each task block, an echo-planar imaging (EPI) sequence will be recorded (72 axial slices, TR = 1500 ms, TE = 34 ms, slice thickness = 2 mm, flip angle = 70°). A diffusion-weighted imaging dataset (64 axial slices, TR = 6000 ms, TE = 52 ms, slice thickness = 2mm, b value = 2,600 s/mm^2; one volume without diffusion sensitization (b value = 0 s/mm^2) per session) will be obtained to assess structural connectivity. The MRI data will be acquired and analyzed by the doctoral student and postdoctoral researcher, under the supervision of the principal investigator.

2.3.2.5 Functional MRI pre-processing and analysis

The fMRI data will be used to assess the activation related to everyday-life ToM and its affective and cognitive components, and provide the landmarks for subsequent connectivity analyses. Pre-processing, image correction and normalization will be performed according to standard procedures implemented in Statistical Parametric Mapping (SPM12, Wellcome Institute of Cognitive Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The pre-processed EPI data will be concatenated over the three recording blocks, and a GLM will be used for statistical analysis of regionally specific effects. The regressors of interest will encode the onsets of each clip, labeled according to the context: non-ToM, affective ToM and cognitive ToM, respectively. The instruction and response time frames will also be assigned distinct regressors. To account for physiological artifacts, six head motion parameters, white-matter and cerebrospinal fluid time series will be included as regressors of no interest. A high-pass filter with 1/256 Hz will be applied and the error term will be modeled as a mixture of a first-order autoregressive process with a coefficient of 0.2 and white noise.

The individual whole-brain level contrasts will be affective ToM versus non-ToM, and cognitive ToM versus non-ToM. Combined random effects analysis on the contrast estimates at the between-subject level will provide the overall activation during everyday-relevant ToM and yield the volumes of interest for subsequent connectivity analyses (8 mm radius around the respective local activation maximum from the fMRI analysis). Comparing the individual contrast estimates in a random effects analysis at the between-subject level will indicate potential regions exhibiting greater specific activation to affective vs. cognitive ToM and vice versa (family-wise error corrected for multiple comparisons at a $p < 0.05$ voxelwise threshold). The activations will be attributed to brain regions using automated anatomical labeling in SPM [158] and the NeuroSynth.org database (http://neurosynth.org).

2.3.2.6 Structural connectivity analysis

Diffusion MRI data will be pre-processed and analyzed using the FMRIB Software Library (FSL4, Oxford Center for Functional MRI of the Brain, UK, http://www.fmrib.ox.ac.uk/fsl). For the pre-processing of

data, to remove voxels located outside the brain, the Brain Extraction Tool [169] will be applied to the T1-weighted anatomical reference image and a volume without diffusion sensitization. Using the FMRIB Linear Image Registration Tool (FLIRT; [170]), we will conduct motion and eddy current correction, coregistration of diffusion-weighted images with the anatomical reference image, and alignment of the diffusion-weighted and anatomical images to the normalized MNI space. Gradient directions will be adjusted accordingly following each FLIRT step. Diffusion parameters for each voxel in every participant will be obtained with Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques with modeling of Crossing Fibers (BEDPOSTX; [171]).

Probabilistic tractography from each volume of interest corresponding to the fMRI activations towards the other volumes of interest will allow computing average two-way structural connection strengths between regions of the network for each individual, used for computation of a group adjacency matrix of relative interregional connection strengths. This will provide a representation of the structural connectivity in the network underwriting ecological ToM.

2.3.2.7 Structurally-informed effective connectivity analysis

We will integrate structural and effective connectivity capitalizing on our recent si-PEB approach [80,93] as further outlined below. Effective connectivity will be assessed using DCM [86,172] as implemented in SPM12. DCM generates multiple alternative models of task-induced variations in the coupling among a set of predefined nodes of a network. Forward generative models predict the expected BOLD response based on a specific neuronal causal model. Bayesian inference is then performed to evaluate the evidence for each model in terms of predicted versus observed BOLD data, with model evidence depending on prior information. Structural connectivity can act as a useful prior for effective connectivity between brain regions, but polysynaptic effective connections between any two regions can also exist in the absence of an underlying, monosynaptic structural pathway [80,92,93].

For the DCM, we will extract regional time series as the first eigenvariate of all activated voxels (at a threshold of $p < 0.05$, uncorrected) within each volume of interest from the fMRI analysis. A one-state, bidirectional and deterministic model including all possible connections between the volumes of interest will be specified and estimated per individual. Subsequently, we will perform a group-level si-PEB analysis, using the structural connection strengths as prior covariance for effective connections. We will specify model families with modular, linearly hierarchical, gatekeeper and distributed setups of information flow in the network. An analytic procedure will estimate the fit for each alternative model, based on the evidence for the model with full connections, searching for the model with the minimal number of connections that would sufficiently explain the observed data [172]. The procedure will provide the optimal integrative connectivity model of the everyday-relevant ToM network including connection strengths. Context-specific effective connectivity changes (all ToM, affective ToM and cognitive ToM) will be modeled as modulation on the connections in the integrative model, and the estimation procedure will deliver the optimal model in terms of the distribution and strength of these modulatory effects. This analysis will unveil the causal and directed interactions within the network for

ecological ToM, and indicate whether some connections may be specifically enhanced or silenced during cognitive or affective ToM.

2.3.2.8 Whole-network level prediction of ToM performance

For assessment of how connectivity relates to ToM performance, the individual whole-network connectivity parameters with a posterior probability of at least 95 % in the optimal model and the MASC scores during the fMRI experiment will be submitted to a canonical variate analysis, as previously implemented [80]. The canonical variate analysis will transform the individual connectivity parameters to canonical vectors representing their contribution in explaining individual MASC performance. A significant mapping between whole-network connectivity and behavior will be retained at $p < 0.05$, indicating a significant advantage in explaining variance over other mapping variants. Three canonical variate analyses will be conducted, for overall, affective and cognitive ToM performance. This approach will allow analyzing the relationships between everyday ToM performance and corresponding whole network dynamics, and appreciating the functional role of specific connections in the context of other connections in the network.

2.4 Schedule and milestones

WP	Task	*Year 1*			*Year 2*			*Year 3*			*Year 4*		
		M 1-4	M 5-8	M 9-12	M 1-4	M 5-8	M 9-12	M 1-4	M 5-8	M 9-12	M 1-4	M 5-8	M 9-12
1	Study setup												
	Patient enrollment												
	VLSM & disconnectome analyses												
	Manuscript preparation												
2	Study setup												
	MRI data recording												
	Data analysis												
	Manuscript preparation												

2.5 Relevance and impact

2.5.1 Scientific relevance

This is the first proposal combining an ecological and holistic assessment of social cognition with cutting-edge integrative lesion and disconnectome mapping and multimodal brain connectivity analyses with the aim of improving our understanding of the distributed brain networks underwriting everyday life ToM in normalcy and pathology. The brain areas and connections necessary for intact everyday life

ToM remain unknown. Making everyday relevance a priority will increase the significance of our findings for improving the life and clinical management of people suffering from deficits in social cognition due to ABI, and other neurological and psychiatric conditions. We also aim at providing an estimate of the proportion of ABI patients with everyday-relevant ToM deficits.

Our novel approaches for multimodal brain network analyses combining structural and effective connectivity allow optimally using the breadth of information afforded by neuroimaging. In particular, effective connectivity can help disentangle the complex interplay between the regions involved in ToM including interactions that may be hidden to activation studies. Finally, both the lesion and disconnectome mapping in ABI patients and the multimodal connectivity analyses in healthy participants are expected to significantly contribute to establishing a consensus on the behavioral and neural dissociations between affective and cognitive ToM. This consensus and a deeper understanding of the affective and cognitive components of ToM would be essential for designing specific efficacious approaches for the neurorehabilitation of social cognition.

The study outcomes will not only be relevant to inform future approaches for neuropsychological rehabilitation of social cognition, but may also serve as a starting point for research on neuroimaging biomarkers for stratification and monitoring of treatment effects in neurorehabilitation of social cognition, and on potential targets and mechanisms for neuromodulation. Overall, this project does not only have the potential to contribute to the optimization of models conceptualizing ToM processing in the brain, but may also have clinical implications for the neurorehabilitation of socio-cognitive deficits.

Moreover, the integrative analyses of the relationships between lesion pattern, multimodal connectivity and behavior will promote the ongoing paradigm shift in cognitive and clinical neuroscience towards multimodal and comprehensive assessment of brain function, with potential implications far beyond the immediate domain of social cognition.

Our findings will be disseminated through publications in international peer-reviewed journals and scientific presentations at national and international conferences.

2.5.2 Broader impact

The overarching aim of our line of research is to improve clinical care for neurological patients suffering from impairments in social cognition, to promote their socio-professional reintegration and to reduce the substantial socio-economic impact caused by ABI-related ToM deficits on our society. According to recent reports [38,173], healthcare practitioners in neuropsychology, memory clinics and neurorehabilitation departments appreciate socio-cognitive impairments as a major issue in their patients, but are also conscious of the lack in assessment and treatment methods. Given international data on stroke and TBI prevalence and the prevalence of socio-cognitive deficits in ABI patients [28], in Switzerland alone, around 7’000 ABI patients present with ToM deficits every year. The present study will contribute to improved early detection and neurorehabilitation of everyday-relevant ToM deficits, and thus reduce the substantial detrimental impact of aberrant social cognition on personal and professional reintegration, and the quality of life of patients with ABI.

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