REGISTERED REPORT (STAGE 1)

Remember as we empathize. Do brain mechanisms engaged in autobiographical memory retrieval causally affect empathy awareness? A combined TMS and EEG registered report

Federica Meconi[1] | John Hodsoll[2] | Zheni Goranova[1] | Giulio Degano[1] | Nicolò Di Lello[3] | Carlo Miniussi[4] | Alessio Avenanti[5,6] | Carmel Mevorach[1]

[1]School of Psychology and Centre for Human Brain Health, University of Birmingham, Birmingham, UK

[2]Department of Biostatistics, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[3]Department of Social and Developmental Psychology, University of Padova, Padova, Italy

[4]Center for Mind/Brain Sciences – CIMeC, University of Trento, Rovereto, Italy

[5]Centre for Studies and Research in Cognitive Neuroscience (CsrNC), Department of Psychology, Campus of Cesena, Alma Mater Studiorum, University of Bologna, Cesena, Italy

[6]Centro de Investigaci on en Neuropsicología y Neurosciencias Cognitivas, Universidad Catolica Del Maule, Talca, Chile

Correspondence
Federica Meconi and Carmel Mevorach, School of Psychology and Centre for Human Brain Health, University of Birmingham, Birmingham, UK.
Email: f.meconi.1@bham.ac.uk (F. M.) and c.mevorach@bham.ac.uk (C. M.)

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Abstract

Social interactions are partly driven by our ability to empathize—the capacity to share and understand others' inner states. While a growing body of evidence suggests a link between past experiences and empathy, to what degree empathy is dependent on our own previous experiences (autobiographical memories, AMs) is still unclear. Whereas neuroimaging studies have shown wide overlapping brain networks underpinning AM and empathic processes, studies on clinical populations with memory loss have not always shown empathy is impaired. The current transcranial magnetic stimulation (TMS) and electroencephalography study will seek to shed light on this neuropsychological puzzle by testing whether self-perceived empathy is causally linked to AM retrieval. Cortical activity, together with self-rating of empathy, will be recorded for scenarios that echo personal experiences while a brain region critical for AM retrieval will be transiently inhibited using TMS before task performance.

KEYWORDS
electroencephalography, empathy, episodic memory, transcranial magnetic stimulation

1 | INTRODUCTION

The experience of sharing similar life events tends to make people feel closer. Bastian et al. (2014) demonstrated that sharing a painful experience within a group increases cooperation between its members. Similarly, empathy for others' suffering can be influenced by spontaneous retrieval of memories details (Vollberg et al., 2021). Remembering or actively imagining others' experiences increases the chances of prosocial acting (Gaesser & Schacter, 2014). Past autobiographical experiences can therefore be an important resource for social interaction. Empathy, which is the ability at the basis of social dynamics, has a multicomponent nature. It entails affective sharing as well as cognitive reasoning on others' inner states (cognitive empathy). These empathy components are dissociable in time course and function, and a recent meta-analysis has confirmed their anatomical dissociation (Lamm et al., 2011; Molenberghs et al., 2012, 2016). Electroencephalography (EEG) studies have revealed that affective sharing modulates event-related potentials (ERPs) in early time-windows: within 250 ms from stimulus onset. Cognitive reasoning mainly modulates the P300 component, which is an electrophysiological index of motivated attention (Fan & Han, 2008; Hajcak et al., 2009; Hajcak & Foti, 2020; Magliero et al., 1984; Meconi et al., 2018; Nieuwenhuis et al., 2005; Palmieri et al., 2021; Sessa, Meconi, Castelli, et al., 2014; Sessa, Meconi, & Han, 2014). Affective sharing (or affective empathy) allows embodiment of others' inner states exploiting simulation mechanisms so that others' states are vicariously experienced in the self. Multiple functional magnetic resonance imaging (fMRI) studies investigating empathy for others' physical pain have repeatedly shown that this is grounded in the ability of the self to feel first-hand pain (Rütgen et al., 2015, 2020). Cognitive reasoning allows to build an accurate representation of the others' inner states. Several studies have demonstrated that healthy adults infer others' inner states by either relying on acquired general semantic knowledge (Pehrs et al., 2017) or on their own past experience (Gaesser, 2020; Gaesser et al., 2018; Mitchell et al., 2006).

In two previous experiments from our laboratory (Meconi et al., 2021), we observed that participants judged their self-perceived cognitive empathy as higher for individuals described to experience similar events as the participants experienced themselves when compared with non-autobiographical memory (AM) contexts. Similarly, Bluck et al. (2013) showed behavioral measures for increased explicit self-perceived empathy when the observers (i.e., the participants) shared past experience of general physical pain with the person described in the task. Thus, these findings on healthy populations support a functional relationship between memory and cognitive empathy.

One reason for the interplay between AM and cognitive empathy might be the extensive functional overlap that exists between the brain networks underpinning these processes. Such an overlap was demonstrated both within the same investigation (Rabin et al., 2009) and when comparing activations across separate investigations (Spreng et al., 2009). These studies showed that AM and cognitive reasoning about others are underpinned by the activation of a brain

Significance

Human empathy is at the basis of our ability to bond and meaningfully interact with other people. Theoretical accounts suggest that we use our own mind as a model to grasp others' feelings. Studies on healthy populations support the idea that our autobiographical memories (AMs) play a role in empathy. However, studies with amnesic patients do not show clear evidence of empathic impoverishment, challenging this intuitive idea that memory is needed to empathize. This research will seek to shed light on this puzzled scenario by directly testing whether empathy causally draws on AM retrieval.

network of frontoparietal and temporal areas that includes precuneus, posterior cingulate, retrosplenial cortex, the temporoparietal junction, lateral and medial prefrontal cortex, the medial temporal lobe, and the lateral temporal cortices. Wagner et al. (2020) further supported this view by showing similar pattern of activation in these brain areas, in the hippocampus, and in the anterior insula for pain perceived in first-hand and empathy for physical pain. Furthermore, hippocampal–neocortical coupling during empathy for pain was larger for higher self-perceived cognitive empathy skills.

However, studies on patients with different memory impairments failed to show clear-cut evidence of a close or causal interplay between AM and self-perceived affective or cognitive empathy. Indeed, only a handful of severely underpowered studies have directly assessed empathic abilities in amnesic patients (Beadle et al., 2013; Rosenbaum et al., 2007). Amnesia follows a focused damage to the hippocampal cortices, which results in impairment of conscious access to long-term memory. Sawczak et al. (2019) showed that patients with medial temporal lobe damage fail to show empathy increases if prompted to build specific representations of others' suffering. Therefore, the very few extant studies did not offer convergent evidence that the inability to consciously access long-term memories reduces either affective or cognitive empathic abilities.

Delineating the brain architectures of empathy and AM retrieval can provide some explanation of why literature does not show converging evidence for impaired empathic abilities in amnesic patients. Most recent meta-analysis and lesion studies have supported the multifaceted nature of empathic abilities. Mechanisms of inner simulation that are implemented by the human mirror neuron system (Molenberghs et al., 2012) and anterior and mid-cingulate cortex (Danziger et al., 2009) underpin affective sharing. Perspective shifting and mindreading that are implemented by a circuit of frontoparietal and temporal areas, which includes the precuneus (Lamm et al., 2011; Molenberghs et al., 2016; Schurz et al., 2014), underlie cognitive reasoning. The retrieval of AM is underpinned by a network of brain areas that does not involve only the hippocampus but also the prefrontal cortex and parietal areas including precuneus, posterior parietal cortex, and the retrosplenial cortex (Boccia et al., 2019;

Cabeza & St Jacques, 2007; Cotelli et al., 2012). Furthermore, according to the systems consolidation account (Antony et al., 2017; McClelland et al., 1995), memories are first dependent on the hippocampus but, with time, can become gradually independent and stably stored in the neocortex (but see also, e.g., Barry & Maguire, 2019; Clark & Maguire, 2016).

Therefore, unravelling the nature of the interplay between memory retrieval and empathy awareness remains an open question. The current study will aim to test the contributory causality between AM reactivation and self-perceived cognitive empathy for others' inner states in healthy participants. We will investigate whether downregulation of a core brain region causally involved in AM reactivation decreases participants' explicit judgments of their cognitive empathy.

Compelling evidence supports the role of precuneus in both AM and cognitive empathy. Hebscher et al. (2020) established in a transcranial magnetic stimulation (TMS) and magnetoencephalography study that the precuneus plays a causal role in AM retrieval. The authors showed in an explicit recollection task that decreasing precuneus activation interferes with neural dynamics of early stages of AM retrieval and the vividness of recollection (see also St. Jacques et al., 2017). In contrast to our knowledge, no study has shown that modulation of precuneus' activation directly reduces any measure of empathic abilities. This therefore enables the proposition that interrupting the precuneus will affect AM retrieval, which in turn will affect cognitive empathy.

While the precuneus is a brain hub that features in a number of networks and has been associated with a number of different functions, several studies have supported the view of the anterior/posterior division of labor within the precuneus (Cavanna & Trimble, 2006; Sajonz et al., 2010). This division attributes self-referential processes, including representation of the self and saliency processing, to the anterior section of the precuneus extending to the inferior parietal lobule (Mevorach et al., 2009, 2010) and long-term memory retrieval processes to the posterior section extending to the superior parietal lobule (Burianova & Grady, 2007). This further supports the identification of the posterior region of the precuneus as the target site for affecting long-term memory processes as in Hebscher et al.,'s (2020) study.

Drawing on this body of evidence, we will conduct a TMS and EEG study in which participants will carry out adapted versions of the tasks used in our previous studies (Meconi et al., 2018; Sessa, Meconi, & Han, 2014) to investigate whether explicit judgments of empathy draw on participants' AMs. The empathy task will show participants a sentence describing a contextual scene for which participants do or do not have an associated AM, followed by a neutral face. Participants' task will be to rate on a 1–6 point scale how much empathy they feel for the individual as depicted in the contextual scene described by the preceding sentence. Therefore, AM retrieval will not be explicitly prompted to preserve the spontaneous nature of its involvement in empathic processes. In our previous study (Meconi et al., 2021) and in a pilot study (reported in the Supporting Information), such a paradigm yielded clear effects of AM on both the behavioral measure, that is the empathy rates, and the ERP signal. In the current study, we expect to replicate these results when the control site is stimulated, see Hypothesis 1 and Hypothesis 2 in the Hypotheses section.

Following Hebscher et al.'s (2020) stimulation protocol, healthy participants will undergo offline continuous theta burst stimulation (cTBS) targeting the precuneus and the vertex as the control area (Cz in the international 10–20 EEG system, see Figure 1A) in counterbalanced sessions. EEG will be recorded while participants perform an empathy task and a task in which they have to picture in their mind's eye the contexts described in the empathy task (i.e., the retrieval task). The experiment will test the causality of AM retrieval ability in healthy participants' empathy in terms of judgments of their empathy awareness and of neural dynamics, that is, cognitive reasoning.

1.1 | Hypothesis

A summary of the hypotheses, the sampling and analysis plans, and the potential caveats for each hypothesis is reported in Table 1.

Hypothesis 1—We expect that precuneus stimulation will interfere with AM retrieval, which will lead to reduced empathy in AM scenarios. As a direct consequence of that, we expect to observe: (a) reduced empathy rates for targets of empathy depicted in AM compared to non-AM context, (b) reduced ERPs differences (specifically on the P3 component) between AM and non-AM after precuneus stimulation when compared to stimulation of the Cz control area between 0.3 and 0.6 s. We expect to replicate previous results when stimulation is delivered to the Cz control site: (a) higher empathy rating for targets depicted in AM when compared to non-AM and (b) ERP differences reflecting the processing of AM versus non-AM (specifically on the P3 component). An unpredicted scenario in this context would be a failure to replicate the memory type effect. Tomova et al. (2017) showed that stress can increase other-oriented responses. It is possible that the TMS procedure together with the time pressure we implement for responses will increase stress in our cohort, and this will negate the contribution of the self-referential thought that is reflected by the AM retrieval.

Hypothesis 2—As the precuneus is also involved in empathic reasoning about others, we predict one possible scenario in which we will observe an overall reduction of empathy rates after precuneus stimulation when compared with the control site.

Hypothesis 3—In order to test for the specificity of the effect of stimulation on the empathy task, participants will perform an additional perceptual task at the end of each trial. The perceptual task will require participants to make a luminance judgment (using a 1–6 point scale reflecting dark/light) regarding the face images. Importantly, the face images used in the empathy task will be equiluminant photos of Caucasian faces in shades of gray. Performance on the perceptual task will enable us to differentiate between empathic and perceptual processing and highlight, if any, a specific effect for reduced empathic (but not perceptual) abilities following inhibition of the precuneus. We would therefore expect no difference on the face luminance rates as a function of the stimulation site and type of memory. The alternative scenario would be to find the stimulation and memory effects on the perceptual judgments. We anticipate this could potentially be related to carryover effects due to task
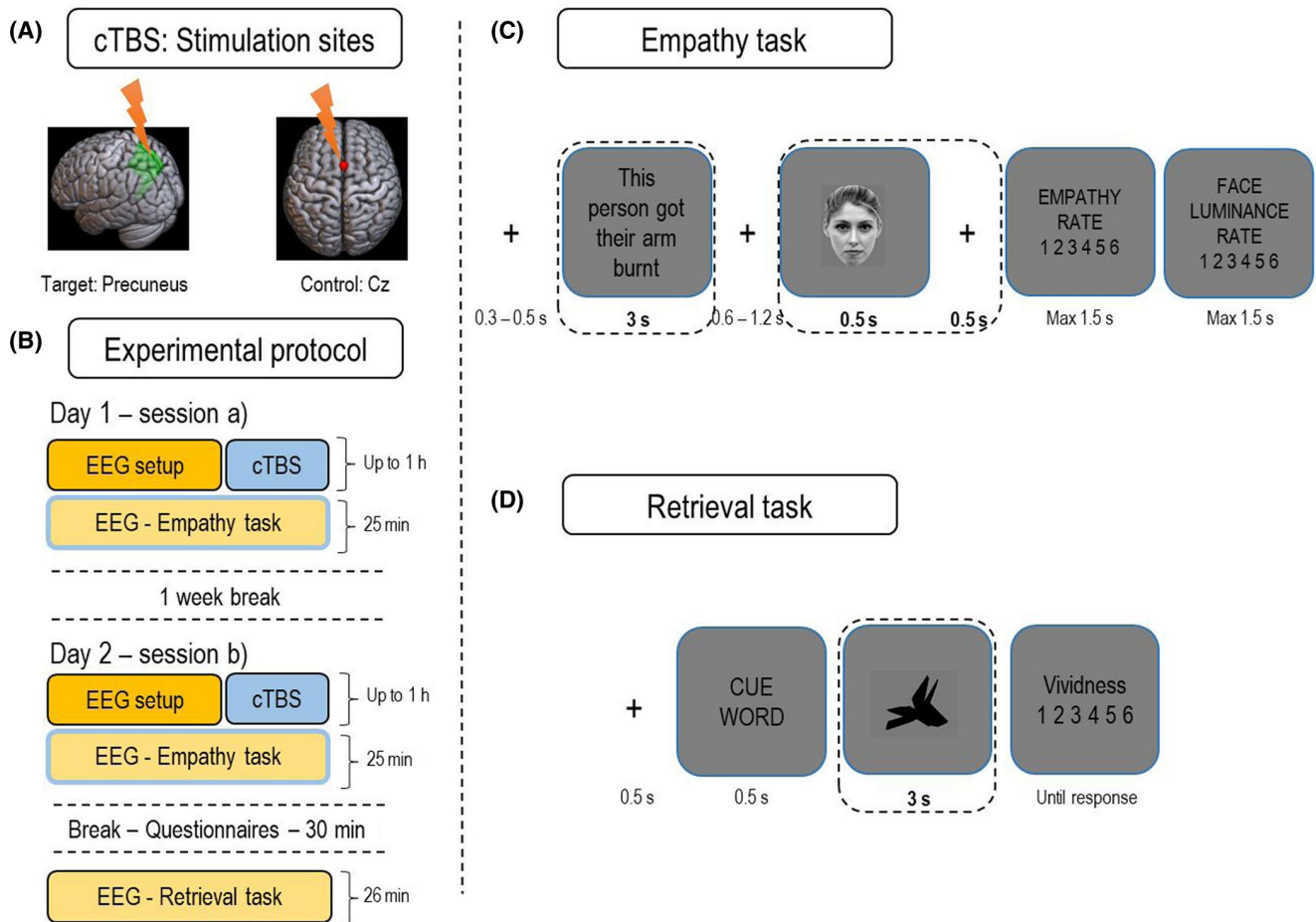
FIGURE 1 Graphical representation of the experimental procedures. (A) Representation of the target and control stimulation sites, Precuneus and Cz, respectively; (B) Schematic representation of the experimental protocol: electroencephalography (EEG) recording will be setup (in orange) and continuous theta burst stimulation (cTBS) (in light blue) will be delivered over one of the sites before the empathy task. During the first day of the experimental session, EEG will be recorded while participants will perform only one half of the empathy task. During the second day of the experimental session, EEG recording will be setup again and cTBS delivered over the other site before the second half of the empathy task starts. EEG recording will be stopped while participants complete the self-report questionnaires during the break. EEG recording will be started again while participants perform the retrieval task, not under the influence of the cTBS. Colors indicated whether the task is performed while only recording EEG (orange), or also targeted by the cTBS (light blue and orange). Estimated time for completion of each part of the experimental procedure is shown. Participants will perform session (a) and (b) 1 week apart from each other. (C) Schematic representation of the empathy task. (D) Schematic representation of the retrieval task. Time durations are for the critical experimental events that are in bold and events highlighted by a dashed line frame

switching costs and strategy-dependent components in task preparation (Altmann, 2004; De Baene & Brass, 2014).

2 | METHODS

2.1 | Pilot data

We ran a sample of five pilot participants (one male and four females) with a slightly different stimulation protocol and target site (the left superior parietal lobule, MNI coordinates [−36 −58 59]) in a repeated measures factorial design with 2 (Emotion: Neutral vs. Painful) × 2 (Memory: AM vs. non-AM) × 2 Face (Neutral vs. Painful) × 2 (Stimulation site: Target$_{left}$ SPL vs. Control$_{right}$ SPL) within-subjects factors. TMS stimulation was delivered trial by

trial over the left and right SPL based on previous findings from our laboratory. We decided to change the stimulation protocol and the target area based on recent compelling findings by Hebscher et al. (2020) that have shown successful alteration of AM retrieval in an explicit recall task after precuneus stimulation. Full details of the pilot design and acquisition procedures are reported in the Supporting Information.

2.2 | Sampling plan

2.2.1 | Power calculation

The main hypothesis of this study (Hypothesis 1) is that interference of AM retrieval, after precuneus stimulation, would cause reduced

TABLE 1 Design table

Question	Hypothesis	Sampling plan (e.g., power analysis)	Analysis plan	Interpretation given to different outcomes
	Hypothesis 1: We expect to interfere with AM retrieval after precuneus stimulation	Power analysis: according to the Cohen's d obtained in the pilot data showing similar results as those predicted in Hypothesis 1, we would obtain 95% of power with 12 participants. We will assess Hypothesis 1 in both sexes	(a) Behavioral effect: Linear mixed-effect model will include as fixed effects: Type of Memory (AM vs. non-AM), and Stimulation Site (Precuneus vs. Cz), their interaction and trials. The random effects structure will include participants and face stimuli	Bayes Factor will be calculated to quantify evidence in favour of the null hypothesis. Null hypothesis: no effect of the type of memory after stimulation over the control site in terms of neither empathy rates nor P3 differences
Does interference with AM retrieval causally reduce self-perceived empathy?	(a) Reduced empathy rates for targets of empathy depicted in AM compared to non-AM context after target area stimulation, when compared to stimulation of the control area	Bayes factor will be calculated to quantify evidence in favour of Hypothesis 1	(b) Cluster-based Montecarlo permutation tests will be performed over the whole scalp over a 1 s time-window on the ERPs time-locked to the onset of the face contrasting AM vs. non-AM contexts for both sites of stimulation	Decreasing precuneus activation prior to asking participants explicit judgments of their empathy for people depicted in AM vs. nonAM contexts fails to show decreased empathy rates for individuals depicted in AM when compared to non-AM contexts and reduced P3 differences between AM and non-AM contexts after stimulation of the target site when compared to the control site. Bayes Factor will be calculated to quantify finding in favour of the null hypothesis
Hypothesis 1: effect of interference with AM retrieval after stimulation of target area, the precuneus	(b) Reduced P3 differences in the 0.3–0.6 s time-window between AM and non-AM after target area stimulation, when compared to stimulation of the control area			Interpretation for not observing evidence in support of Hypothesis 1 would also depend on replication results
	Hypothesis 1: We expect to replicate previous results when stimulation is delivered to the Cz control site	Power analysis: according to the lowest Cohen's d obtained in previous findings (d = 0.51) we would obtain 95% of power with 45 participants	(a) Linear mixed-effect model will include Type of Memory (AM vs. non-AM), and Stimulation Site (Precuneus vs. Cz), their interaction and trials, as fixed effects. The random effects structure will include participants and face stimuli	Interpretation: Failure of the replication of previous findings. Tomova and colleagues (2017) showed that stress can increase other-oriented responses. Stress caused by TMS itself and time pressure caused by restricted time-window allowed for self-perceived empathy judgements might have the effect of reducing the self-referential thought that is reflected by the AM retrieval

TABLE 1 (Continued)

Question	Hypothesis	Sampling plan (e.g., power analysis)	Analysis plan	Interpretation given to different outcomes
Does interference with AM retrieval causally reduce self-perceived empathy? Hypothesis 1: replication of previous findings after stimulation of control site, Cz	(a) Behaviour: higher empathy rating for targets depicted in AM when compared to non-AM	Data inclusion: • Excellent English proficiency; • 18–35 yo sex balanced Caucasian participants; • normal, or corrected-to-normal, vision; • meet TMS and MRI safety guidelines; • right handed; • no history of neurological, psychiatric or developmental disorder; • not on any psychotropic drug medication; • normal hand mobility; • Past experiences of intense physical pain	(b) Cluster-based Monte-Carlo permutation tests will be performed over the whole scalp over a 1 s time-window on the ERPs time-locked to the onset of the face contrasting differential P3 amplitudes for AM minus non-AM contexts between stimulation sites	Alternative scenarios include Hypothesis 2: as precuneus is also involved in empathic reasoning about others, we might observe an overall reduction of empathy rates across both contexts after precuneus stimulation when compared with control site. We will provide BF to quantify evidence in favour of this alternative hypothesis in the same way as for Hypothesis 3
	(b) ERP: ERP differences reflecting the processing of AM vs. non-AM (specifically on the P3 component)	Data exclusion: • Scoring less than 70% in accurately responding whether they saw a painful or neutral face in the empathy task; • participants with EEG data that leads to severe artefact rejection (e.g., more than 60% of trials) in any of the tasks; • TAS-20 in the clinical range of alexithymia (i.e., >60); • incomplete data due to technical problems or withdrawal from the experimental session		
Is stimulation protocol affecting precuneus specific processes?	Hypothesis 3: We expect to interfere with precuneus related but not unrelated processes, i.e., face luminance perception	Bayes factor will be calculated at when full sample is collected (N = 45). We will provide the Bayes factor of the effect of stimulation on the type of rates (empathy vs. perceptual) in order to quantify evidence in favour of the null hypothesis. If the BF does not show strong evidence in favour of the null hypothesis (BF: 1/30–1/10) we will continue data collection for the empathy task only	Linear mixed-effect model will include as fixed effects: Type of Memory (AM vs. non-AM), Stimulation Site (Precuneus vs. Cz), type of rate (empathy vs. perceptual), their interaction, and trials. The random effects structure will include participants and face stimuli	Possible carry over effects due to task switching costs and strategy dependent components in task preparation will be discussed (Altmann, 2004; De Baene & Brass, 2014)
Hypothesis 3: Neutral outcome—specificity of observed effects	We expect to observe empathy but not face luminance rates modulations after precuneus stimulation	Data inclusion criteria: same as in Hypothesis 1 section • Scoring less than 70% in accurately responding whether they saw a painful or neutral face in the empathy task; • TAS-20 in the clinical range of alexithymia (i.e., >60); • incomplete data due to technical problems or withdrawal from the experimental session		

empathic feelings as expressed on a behavioral level by the empathy rates, that is, a Memory × Stimulation site interaction.

This study uses the same methodological approach as two previous experiments conducted in our laboratory. The sample of both experiments was composed of 28 healthy students. This study is a 2 (Memory: AM vs. non-AM) × 2 (Stimulation site: Target vs. Control) within-subject factorial design. The critical result obtained with the pilot data was a Memory × Stimulation site interaction $F(1, 4) = 5.565$, $\eta_p^2 = 0.582$. Further exploration of this interaction showed (even though nonsignificant) reduced differences between empathy rates for individuals depicted in AM than those depicted in non-AM contexts after stimulation of the target area ($M = 0.440$, $SD = 0.664$) when compared with the control area ($M = 0.749$, $SD = 0.850$). We calculated mean differences for the AM and non-AM rates for each site of stimulation and then performed a paired sample t test between the differential scores obtained in each site ($M_d = -0.30679$, $SD_d = 0.29080$, correlation between measures: $r = 0.956$, $t(4) = 2.359$, $p = 0.078$, CI = [−0.668, 0.054]) with a large effect size Cohen's $d = 1.06$.

We entered G-power 3.1 with the differential values of the means ($M_{diff} = -0.30679$) of the standard deviations ($SD_{diff} = 0.29080$) and correlation between the measures ($r = 0.956$) for the t test obtained in the pilot participants where the relevant effect was observed, Cohen's $d = 1.06$ and $\alpha = 0.05$. We obtained that we could achieve 95% of power with 12 participants.

In our previous EEG experiment (Meconi et al., 2021), the size of the main effect of increased empathy ratings for AM compared with non-AM contexts was Cohen's $d = 0.89$, as obtained in a sample of mainly female participants (four males). The finding was replicated in the second fMRI experiment from the same project with Cohen's $d = 0.51$ as obtained in a sample composed of 11 males and 17 females. We also observed ERP differences, such as the fact that AM elicited larger P3 when compared to non-AM after the onset of the face, in response to the processing of the contextual scene. We calculated average amplitudes of ERPs in response to AM and non-AM contexts and obtained a large effect size of Cohen's $d = 0.83$ (4 males).

While these previous investigations included different rates of male/female participants, we used G-power 3.1 with the parameters extracted in our more balanced previous cohort. It is therefore also our intention in this study to balance biological sex and recruit participants accordingly, and thus, our power calculation is targeted at identifying effects across a balanced cohort of female/male participants. We entered the differential values of the means ($M_{diff} = 0.35$) of the standard deviations ($SD_{diff} = 0.6991$) and correlation between the measures ($r = 0.618$) for the t test that showed the lowest effect size, Cohen's $d = 0.51$ and $\alpha = 0.05$ (which was obtained with the balanced cohort) into G-power 3.1.

Consequently, our power analysis revealed that for the smallest effect size, we would achieve 95% of power with 45 participants. Further investigation of the effects in male and female participants will be conducted as part of an exploratory path of analysis.

Based on these power calculations, our study will have enough power to identify stimulation effects in male and female participants

separately (given a biological sex-balanced cohort of 45 participants). As such, we will assess this hypothesis across the whole cohort as well as separately in female and male participants.

As for Hypotheses 2 and 3, we will calculate the Bayes factor (BF) once data from the 45 participants have been collected. We will provide the BF for the absence of the effect of stimulation only (Hypothesis 2) and for the absence of the effect of stimulation and memory on the type of rates (empathy vs. face luminance) in order to quantify evidence in favor of the null hypothesis. If BF does not show strong evidence in favor of the null hypothesis (BF: 1/30–1/10), we will report it and collect more behavioral data, for the empathy task only, until at least moderate evidence is achieved.

2.2.2 | Participants

We will recruit participants until a sex-balanced final sample of 45 participants (22 males) is reached after the data exclusion, as described in the data exclusion criteria section.

The target population is 22 Caucasian male and 23 Caucasian female participants between 18 and 35 years of age with excellent English proficiency, normal motor ability of the hands (e.g., no tremors in the hands), and normal, or corrected-to-normal, vision. Ethnicity is required in order to prevent ethnicity bias in the empathic processes (Avenanti et al., 2010; Sessa, Meconi, Castelli, et al., 2014; Sheng & Han, 2012; Xu et al., 2009). Anatomical scans from all the participants will be collected from the servers of the University of Birmingham or acquired before the experimental session. This will be done to identify the target and the control area on each participant's brain. All participants will be screened in accordance with TMS (Rossi et al., 2020) and MRI safety guidelines of the Centre for Human Brain Health at the University of Birmingham and all will need to be able to report at least six life episodes of intense physical pain. Participants should also be right handed, have no history of neurologic, psychiatric, or developmental disorders, and should not be on any psychotropic drug medication.

2.2.3 | Volunteers pre-screening

The study requires several inclusion criteria that are listed in the participants recruitment advertisements approved by the ethics committee. Prior to the experimental session we will contact volunteers as soon as they express their interest in participation. In this pre-screening phase, we will ask the participants a series of questions from which we will collect the information on whether they have or have not experienced in their life episodes of intense physical pain, and episodes of neutral content (e.g., life episodes, we refer the reader to the Stimuli and Procedure section). This phase has the crucial aim to detect the AM and non-AM episodes that will be used as stimuli in the empathy task. Therefore, each participant will have their own set of stimuli. During this phase, it will also be checked that the volunteer meets the TMS and MRI safety inclusion criteria. This phase is critical

to determine whether a volunteer is eligible to partake in the research study. If we are unable to collect the whole set of AM and non-AM episodes or if it is unsafe for the volunteer to undergo the experimental session, they will not be accepted as a participant.

2.2.4 | Data exclusion criteria

Participants for whom responses to the empathy rate were not collected in less than 70% of trials will be excluded from the sample. Participants with EEG data that leads to severe artefact rejection (e.g., more than 60% of trials) in one of the two tasks will be excluded from the sample for analysis of the EEG data. Participants whose score in the TAS-20 falls in the clinical range of alexithymia (i.e., >60) will be excluded from the sample. Participants who do not complete the experimental session for voluntary withdrawal or because of technical issues with the EEG or the TMS equipment will be excluded from the sample. Inability to collect individual's anatomical scan will not constitute exclusion from the sample.

Individuals' luminance rates will be included in the analysis independently of whether their EEG data were excluded from further analysis for poor quality.

2.3 | Design

2.3.1 | Stimuli and procedure

Figure 1B depicts a schematic representation of the within-subjects experimental protocol adopted for this study. Participants will perform two tasks—the first being the empathy task and the second a retrieval task. cTBS will be delivered offline in two separate sessions for each stimulation site before starting the empathy task. The order of the stimulation sites will be counterbalanced across participants. The sessions will be run on two different days, 1 week apart from each other. The retrieval task will always be performed only in session (b), after both halves of the empathy task have been completed.

The tasks will be programed with the Psychtoolbox on a computer running MATLAB 2019b on Ubuntu 18 LTS. All the stimuli will be presented on a gray background of a 24″ computer screen with a refreshing rate of 75 Hz at a 1,280 × 1,024 resolution.

One critical manipulation in this task is that the targets of participants' empathy are described as first-hand experiencers of a context for which participants have or do not have a related AM. Therefore, to take part in this research, participants will be screened prior to the experimental session with an online form in order to collect a set of episodes that belong and that do not belong to their AM. Inability to list any previously experienced episode of intense physical pain will prevent participation in this study. A set of six episodes of intense physical pain for which participants have and do not have a related AM will be identified for each participant to be tailored and used as stimuli in each experimental session.

2.3.2 | The empathy task

The stimuli for the empathy task will be contexts described by sentences, followed by faces. Participants' task will be to rate how much empathy they feel for the person as depicted in the preceding context. The faces will be a set of 12 identities, 6 males and 6 females with a neutral facial expression. The faces will be in shades of gray and equalized for luminance with the SHINE (spectrum, histogram, and intensity normalization and equalization) toolbox (Willenbockel et al., 2010) for MATLAB. The sentences will be describing contexts in which a person feeling physical pain for which participants have a related AM. Episodes of physical pain that do not belong to participants' AM will be used for the non-AM contextual scenes. The scenes will be described by a sentence with a fixed syntactic complexity: "This person got – […]," for example "This person got their right arm broken." Each participant will be presented with a tailored set of 12 scenes (6 painful AM and 6 painful non-AM).

In the empathy task (Figure 1C), each trial starts with a fixation cross (0.3–0.5 s) followed by the sentence (3.0 s) describing an AM or non-AM contextual scene. After a second fixation cross (0.6–1.2 s), a neutral face will be presented on the screen (0.5 s) followed by a third fixation cross (0.5 s). Participants' task is to rate how much empathy they feel for that person in that scene on a 1–6 point scale. The empathy rate will be provided by pressing one of six response keys on the computer keyboard ("s," "d," "f," "j," "k," and "l"), with "s" = "1: no empathy at all" and "l" = "6: a lot of empathy." Responses will be self-paced within a fixed time-window of up to 1.5 s. Lastly, participants will be asked to judge the luminance of the face image on the same 1–6 point scale as for the empathy rates. The face luminance rate will be provided with the same 6 response keys with "s" = "1: very light" and "l" = "6: very dark." Responses will be self-paced within a fixed time-window of up to 1.5 s.

The empathy task will be composed of 288 trials, 144 per stimulation site. Each half of the task will present all the conditions over 6 blocks of 24 trials in a pseudo-randomly intermixed order to balance their distribution over the whole task. Self-paced breaks will interleave the blocks. Each half of the task will be performed under 25 mins. Blinding is involved in this study as participants will not be aware of which TMS session delivers pulses over the target or the control area and we will not disclose the reasons why we asked participants about their life episodes in the pre-screening phase until the whole study is completed.

2.3.3 | The retrieval task

For the retrieval task (Figure 1D), one cue word per each episode presented in the empathy task will be created. For example, we could use "arm" as a cue-word for a sentence like "This person got their right arm broken" and "sting" for "This person got a bee sting." The cue words will be followed by an abstract figure, one per type of memory (one figure for all the AM scenes, another figure for all the non-AM scenes).

For this purpose, a unique combination of one pair of shapes will be used for each participant. The shapes will be two random polygons with an equal number of black pixels. All the stimuli, the cue words and the abstract figures will be presented on a gray background.

Each trial will begin with the presentation of a fixation cross (0.5–1.5 s). A cue word will then be shown for 0.5 s and followed by one of the corresponding four shapes (3.0 s). The task is to picture the scene cued by the word during the presentation of the shape as vividly as possible. Participants will then be asked to rate the vividness of the mental image they were required to picture in their mind's eye by pressing one of the six response keys ("s," "d," "f," "j," "k," and "l"), with "s" for "not vivid at all" to "l" for "very vivid."

The task will be subdivided into four blocks of 66 trials. Self-paced breaks will interleave the blocks. Conditions will be pseudo-randomized to balance their distribution over the 264 trials. The task will take not more than 26 min to be completed. The retrieval task will act as a localizer to extract the neural fingerprints of the scenes and to train an EEG pattern classifier that will probe the data recorded during the empathy task in an exploratory path of analysis. Prior to this task, participants will receive no stimulation.

2.3.4 | Questionnaires

A series of questionnaires will be administered at the end of the empathy task in session b. We will assess dispositional empathic resources with the Interpersonal Reactivity Index (Davis, 1983) and the Empathy Quotient (Baron-Cohen & Wheelwright, 2004). Lesion studies showed that amygdala damage produces impairments in the abilities of retrieving unpleasant memories, recognizing others' unpleasant facial emotions and, critically, recognizing one's own unpleasant memories as actually being unpleasant (Buchanan, 2007). Therefore, we will also assess the ability of participants to report their own emotions with the Toronto Alexithymia Scale, TAS-20 adults form (Bagby et al., 1994); participants who will report clinical degree of alexithymia will be excluded from the sample. Questionnaires will provide descriptive characteristics of the dispositional empathy and emotional resources of the sample. Correlational analysis between dispositional empathy and neural and behavioral data will be part of the exploratory path of analysis. Finally, we will assess the age, vividness, and accuracy confidence of the AMs chosen for each participants according to what they reported in the screening phase with the items of the Autobiographical Memory Questionnaire (Rubin et al., 2003). The questionnaire session will take about 30 mins to complete.

2.4 | Data acquisition and TMS protocol

2.4.1 | TMS protocol

Following Hebscher et al. (2020), participants will receive the offline stimulation to their left precuneus (MNI -14, -66, 56) as the target area and to the Cz as the control site in two experimental sessions.

The intensity of stimulation will be determined for each participant at the beginning of the first session. Individual resting motor threshold (rMT) will be measured as the lowest intensity able to produce motor evoked potentials (MEPs) in at least 50% of the trials. MEPs will be recorded from the right first dorsal interosseous muscle. A Magstim Rapid stimulator (MagStim, Whitland, UK) with a 70-mm figure-8 (D70 alpha flat coil) will be used to deliver a modified cTBS at 80% of individual rMT, for about 40 s. The cTBS protocol will consist of 600 pulses arranged into bursts of three pulses delivered at 30 Hz, which are delivered every 200 ms. Individual anatomical scans will be acquired before the experimental session on a 3T magnetic resonance imaging scanner (MAGNETOM Prisma Siemens). In cases where participants have already had an anatomical scan acquired at the Centre for Human Brain Health using similar parameters, we will use the previously acquired scan. The target area will be translated from MNI space onto each participant's T1 anatomical scans and the coil position will be guided using Brainsight Frameless Stereotaxic software (Rogue Research, Montreal, Quebec, Canada). The position of the coil and the subject's head will be monitored using a Polaris Optical Tracking System (Northern Digital, Waterloo, Ontario, Canada). An adjustable frame will allow the coil to be held firmly and tangentially to participants' heads with the handle pointing posteriorly. Participants will rest their heads on a chin and forehead rest so that head movements will be kept negligible.

2.4.2 | EEG procedure

EEG will be recorded while participants perform the empathy and the retrieval tasks using a 64 channels TMS compatible system (BrainAmp DC Brain Products GmbH, Germany) and a TMS compatible cap (BrainCap Brain Products GmbH, Germany). The participants will wear the EEG cap during the TMS stimulation. Three electrodes of the cap will be placed around the eyes, one below the left eye and two on the external canthi to record blinks and saccades, respectively. Continuous data will be sampled at 1,000 Hz. The ground electrode will be placed at Fpz and the online reference will be placed at FCz. The impedance will be kept below 10 kΩ for all skin–electrode interfaces. Data will be recorded with a bandpass filter of 0.01–80 Hz; a notch filter of 50 Hz will be applied offline. Offline data will be downsampled to 500 Hz and independent component analysis (ICA) will be applied to correct for the eye movements. Data will be re-referenced offline to the average reference after the ICA. EEG data will be analyzed with MATLAB (©MathWorks, Munich, Germany) using the open-source FieldTrip toolbox (http://fieldtrip.fcdonders.nl/) and in-house Matlab routines that will be made available as open resources. All preprocessing steps will be performed blind to the conditions of the experiments.

2.5 | Data analysis

2.5.1 | Behavior

Empathy rating and perceptual scores for the empathy and perceptual tasks will be summarized with the overall mean and frequency of

response per rating level according to experimental condition, along with the number of missing responses per condition. The rating responses will be treated as continuous to facilitate using linear mixed models for the primary analysis.

For the primary analysis (Hypothesis 1), responses will be entered a linear mixed-effect model with fixed effects of type of memory (AM vs. non-AM), stimulation site (Precuneus vs. Cz), and a two-way interaction as a contrast between the size of the AM difference (AM vs. non-AM) according to stimulation site. Trial number (as a continuous variable) will also be included as a fixed effect to allow for performance to change over the course of the experiment (e.g., from practice effects). To account for the dependency between repeated measures, the model will include random effects for participants and faces. Random intercepts will be included for both participants and faces. Models will be estimated with REML and likelihood ratio tests will compare different random effects structures with random intercepts only being the minimal. Finally, to account for potential dependency across trials, the model will include marginal terms to model the autocorrelation between residuals, with responses to adjacent trials tending to be more similar than trials further away in the sequence. Model criticism will involve examining level 1 and 2 residuals for normality and the identification of influential observations using Cook's distance.

In order to test the specificity of stimulation on empathy rates, a second model will extend the first to include perceptual ratings as an outcome and fixed effects of the type of rate (Empathy vs. Perceptual) along with the type of memory (AM vs. non-AM), stimulation site (Precuneus vs. Cz), and their interactions. A three-way interaction between rating type, memory type, and stimulation site will not be sufficiently powered for a conclusive hypothesis test and so the focus of this assessment will be standardized regression coefficients (ES) and 95% confidence intervals. For both analyses, these responses will be collected for each participant independently of the quality of their EEG data.

A third model will be formulated for the vividness rates collected in the retrieval task. The fixed effects will include the type of memory (AM vs. non-AM). The random effect structure will include participants and trials as random intercepts. Vividness rates and EEG data collected in the retrieval task will be part of an exploratory path of analysis.

Eta squared and standardized regression coefficients will be reported as effect sizes.

2.5.2 | Univariate ERPs analysis

For the empathy task, EEG data will be first segmented into epochs of 3 s, starting 1 s before the onset of the face. ERPs will be computed time-locked to the onset of the face to account for the involvement of memory in the empathy task dependent on the site of the stimulation. To this end, spatiotemporal cluster-based Monte Carlo permutation tests as implemented in Fieldtrip will be performed over the whole scalp over a 1 s time-window. Clusters will be defined with a minimum of three neighbor channels. The neighborhood of channels will be determined with a triangulation method. The number of

permutations will be set to 1,000. ERPs will be time-locked to the onset of the face contrasting AM versus non-AM contexts for both sites of stimulation. The accepted p value will be set to 0.05.

For the retrieval task, EEG data will first be segmented into epochs of 5 s, starting 1 s before the onset of the shape.

Since participants will undergo two sessions in two different days, all the data will be normalized with z-scores.

An alternative approach to analyze ERPs amplitudes will be the linear mixed-effects model approach. Mean amplitudes in the critical 0.3- to 0.6-s time-window will be calculated for each condition and be the dependent variable. The model will include the same fixed effects (type of memory, stimulation site and their interaction, trials) and the same random structure (participants and faces as random intercepts), as for the empathy rates.

2.5.3 | Potential caveats

We anticipate completing data collection between September 2021 and June 2022; however, this will be subject to the evolving scenario of the current COVID-19 pandemic, which is an unpredictable variable.

The main aim of this study is to investigate whether decreasing activation of a core brain area of AM retrieval interferes with participants' empathy awareness. Although specific AMs of the participants will be involved in the study, it is important to specify that the offline stimulation will decrease the activation of the target brain area in a non-specific way. Thus, brain stimulation is expected to reduce the ability to retrieve AMs in general, not with respect to a specific AM. To target a specific AM a different stimulation approach may be used where stimulation is applied during a limited time-window. Such an approach represents a path for future investigation. This will be discussed as a potential limitation of the study in the Discussion section.

This study does not have sufficient power to draw conclusions regarding possible differences in empathy processes related to biological sex. As the latter is a between-group studies, sample sizes for interaction effects would need to be significantly bigger. Nevertheless, we will be able to assess and compare descriptively the main hypothesis of the current study (Hypothesis 1) separately in males and females using means and 95% CI as well as across the whole cohort.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

Ravenna, Italy [339bis/2017] and Italian Ministry of Education, University and Research [2017N7WCLP].

ETHICS INFORMATION

The research complies with all relevant ethical regulations; all methods have been approved by the Birmingham University Ethics Committee (ERN_18-1399B). Informed consent will be obtained from all subjects participating in this research. Participants will be recruited using the University of Birmingham Research Participation scheme as well as through flyers and posters distributed on and off campus. All participants will be reimbursed for participation with cash (7£/h) or course credits (1c/h).

COMPETING INTERESTS

The Authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Methodology, Project Administration, Resources, Software, Visualization, Writing – Original Draft and review & editing, F.M.; *Conceptualization, Project Administration, Resources, Supervision, Writing – Original Draft and review & editing*, C.Me; *Formal Analysis, Methodology, Writing – review & editing*, J.H.; *Investigation*, D.S., *Investigation, Visualization*, N. D. L.; *Formal Analysis*, G. D. and *Conceptualization, Writing – Original Draft and review & editing*, C. Mi and A.A.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/jnr.24906.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be openly available on the OSF database along with the pre-registered pilot data, already available, at https://osf.io/nya6k/?view_only=f3ab699328 05405ab8c1bf6b3f70602f.

CODE AVAILABILITY STATEMENT

Matlab codes will be openly available on the OSF database at https://osf.io/nya6k/?view_only=f3ab69932805405ab8c1bf6b3f70602f.

ORCID

Federica Meconi https://orcid.org/0000-0003-0214-9864
John Hodsoll https://orcid.org/0000-0001-7546-9901
Giulio Degano https://orcid.org/0000-0003-1540-780X
Carlo Miniussi https://orcid.org/0000-0002-5436-4745
Alessio Avenanti https://orcid.org/0000-0003-1139-9996
Carmel Mevorach https://orcid.org/0000-0003-1596-1026

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

FIGURE S1 Schematic representation of the pilot paradigm. A series of three TMS pulses was delivered at the offset of the face. TMS targeted the left SPL (i.e., the target area) and the right SPL (i.e., the control area) for each half of the empathy task, respectively, in a counterbalanced order across participants

Transparent Science Questionnaire for Authors

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