

Fachbereich Erziehungswissenschaften und Psychologie der
Freien Universität Berlin

**Neural Network Dynamics During Socio-Emotional
Cue-Integration**

Dissertation

Zur Erlangung des akademischen Grades Doktorin der Philosophie
(Dr. Phil.)

Doctor of Philosophy (Ph.D.)

im Fach Psychologie

Vorgelegt von Dipl. Psych. Corinna Pehrs

Berlin, 2015

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Disputationsdatum: 5. November 2015

Gemeinsame Promotionsordnung zum Dr. phil. / Ph.D. der Freien Universität Berlin vom 2. Dezember 2008 (FU-Mitteilungen 60/2008)

To my parents

Wolfgang & Rita Pehrs

*Whilst part of what we perceive comes through our senses from the object before us,
another part (and it may be the larger part) always comes out of our own head.*

William James (1890)

Acknowledgements

I am very indebted to all the people who have supported me in writing this thesis. First, I want to thank my supervisors, Stefan Koelsch and Lars Kuchinke, for their trust, their scientific advice and their guidance in developing my scientific interests. Furthermore, I'd like to thank Arthur Jacobs, Hauke Heekeren, Malek Bajbouj from the former Cluster of Excellence Languages of Emotion at Freie Universität Berlin. Special thanks goes to the Graduate School of the Cluster, which provided a stimulating research context and a valuable interdisciplinary training on emotion research.

From Freie Universität, I thank Sabine Aust, Mareike Voget, Kathrin Bethke, Daniela Schönle, Lorna Schlochtermeyer, Jan Hendrik Bakels, Isabel Bohrn, Ulrike Altmann, Moritz Lehne, Lila Taruffi, Shuang Guo, Stavros Skouras, Philipp Engel, Alfred Stumm, Rousbeh Djahangiri, Melanie Feeser, Yan Fan, Felix Blankenburg, Ryszard Auksztulewicz, Carmen Morawetz and Dar Meshi. I also thank Evgeniya Kirilina, Christian Kainz and Jürgen Baudewig from the Dahlem Institute for Neuroimaging of Emotion for their help with fMRI measurements and all the participants, who took part in the studies.

I am especially grateful to Lorenz Deserno, Tom Fritz and Jamil Zaki for their fruitful collaboration. In addition, I thank Christiane Rohr, Hadas Okon-Singer, Daniel Margulies and Thorsten Kahnt.

During my PhD, I spent one year at the Stanford Psychophysiology Laboratory of James Gross. For this great opportunity, I would like to thank the Direktaustausch from Freie Universität Berlin. I am truly indebted for a wonderful time and an intriguing research experience to Andrea Samson, James Gross, Valeria Manera, Ihno Lee, Kathryn Kalaf, Sylvia Kreibig and Ursula Beermann.

And of course, I'd like to thank my friends and important people for understanding and emotional support, specifically Dada Held-Poschardt, Ann Kristin Kröger, Magdalena Dudel, Nigar Stücker, Sebastian Infante, Ute Burmester, Anne Lorenz and Hugues Lantuit.

I dedicate the dissertation to my parents, Rita and Wolfgang Pehrs, for their ceaseless trust and loving support. Finally, I would like to thank with all my heart my sister, Christina Pehrs, for giving me strength and encouragement and for accompanying this work with humor, presence and valuable advice.

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Summary

Everyday social interactions require a constant integration of external socio-emotional cues in order to adequately react and adapt to conspecifics, which is fundamental for engaging in fruitful collaborations and joyful interactions. The present dissertation thesis aims to elucidate the underlying neural integration mechanism by testing the modulatory impact of different cues from separate modalities (visual, auditory and contextual) on network dynamics. For this purpose, naturalistic stimuli, i.e. film clips from feature films, were presented to healthy study participants in the fMRI scanner while the film clips were systematically manipulated with regard to their combination with music and written context information. Brain networks were investigated by means of advanced connectivity analysis, namely dynamic causal modeling (DCM) in combination with Bayesian model selections (BMS) for measures of effective connectivity, indicating a directed change of connectivity, and seed-based resting state functional connectivity (RSFC) for measures of functional connectivity (undirected connectivity). Three studies investigated the impact of the cue configuration on socio-emotional processing, specifically the elicitation of discrete emotions and empathic concern for the movie characters as well as the use of experiences from one's past to infer other people's mental state, i.e. episodic simulation. A fourth project commented on the Quartet Theory of Human Emotions (QT) and discussed dysfunctional cue-integration as biomarker for autism spectrum disorder (ASD), a psychiatric disease with impairments in socio-emotional processing preceding the film clips.

Study 1 focused on the modulatory impact of music and presented kissing scenes from romantic comedies either with happy music, sad music or without music. Study 2 not only focused on the modulatory impact of music but also on the modulatory impact of context information. For this purpose, empathic film clips depicting close-ups of sorrowful movie characters were presented either with sad music or without music and either with a sad, a neutral or without written context information. Study 3 applied the same task as Study 2 and additionally measured brain activity during rest in the same set of participants. Study 3 investigated the connectivity of two brain regions, which are key for different memory types, the temporal pole (TP) for semantic memory (SM) and the hippocampus (HP) for AEM,

assuming an integration of both memory systems as an underlying mechanism for episodic simulation, triggered here by context information.

Study 1 and Study 2 demonstrated the strong power of music in emotion elicitation. Music significantly increased the participant's emotion towards the timbre expressed by the music (sad or happy music accompanying the kissing scenes); a co-presentation of sad music also increased the participant's empathic concern for the movie characters. Connectivity analyses have shown that the anterior superior temporal gyrus (aSTG) integrates multisensory information and suppresses neural propagation of preprocessed visual information (in the fusiform gyrus (FG)) to the amygdala, which was more pronounced during sad music. Study 2 demonstrated the significant impact of sad written context information for the participants' empathic concern. An emotion effect of context was found in the temporal pole (TP), a brain region involved in domain-general semantic and socio-emotional processing. Connectivity analyses revealed that context information induced top-down modulations of the TP to lower-level processing within the ventral visual stream (FG), which were moreover significantly increased by music. Study 3 discovered interactions between neural structures implicated in different memory types (SM and AEM) as a pillar for mnemonic integration and episodic simulation. Evidence for inter-hemispheric connectivity from left aHP to the right TP was consistently provided for two different functional states (rest and task).

These findings were used to propose a tentative neurobiological model of socio-emotional cue-integration. The model suggests several neural integration mechanisms for socio-emotional cues, some of which were supported by the results of the present thesis. We showed that convergence regions (aSTG and TP) integrate multisensory information on different hierarchical levels and exert neuromodulatory influence. They gated the connectivity of brain regions involved in emotion processing (FG and AMY) and top-down modulated activity in modality specific cortices (FG) as a function of task demands. This is consistent with TP's role as a semantic hub and the concept of top-down facilitation during object recognition. In addition, mnemonic integration enables episodic simulation and relies on effective connectivity between functional and lateral specialized brain regions, which are key for different memory types.

In summary, this dissertation provides strong evidence for the modulatory impact of socio-emotional cues on experienced emotions and underlying network dynamics. It demonstrates the power of music in emotion elicitation, redefines the

role of the TP in socio-emotional cognition and highlights the importance of memory processes for social cognition. Emerging mechanisms were integrated in a neurobiological model providing the framework for understanding cue-integration and generating research questions, specifically for psychiatric disorders with impairments in the social domain, which might be conceived as neurocognitive integration disorders.

Keywords: default network, dynamic causal modeling, emotion, empathy, episodic simulation, film, hippocampus, memory, multisensory integration, social cognition, temporal pole

Zusammenfassung

Soziale Interaktionen sind für die Lebenswelt des Menschen von elementarer Bedeutung. Während dieser werden permanent externe sozio-emotionale Informationen, wie z.B. Gesichter und Dialoge im Gehirn integriert. Eine effiziente Integration ist die Voraussetzung dafür, sich auf den Interaktionspartner einstellen zu können und sich angemessen zu verhalten.

Diese Dissertation untersucht den modulierenden Einfluss von Informationen (*Cues*) aus unterschiedlichen Modalitäten (visuell, auditorisch, kontextuell) auf neuronale Netzwerke. Dazu wurden naturalistische Stimuli, Filmclips aus Spielfilmen, gesunden Probanden im funktionellen Magnetresonanztomographen gezeigt. Die Stimuli wurden hinsichtlich ihrer Komposition systematisch manipuliert und entweder mit oder ohne Musik und mit oder ohne Kontext-Informationen präsentiert. Mittels anspruchsvoller Konnektivitätsanalysen wurde die Modulation neuronaler Netzwerk-Dynamiken durch unterschiedliche Cue-Konfigurationen untersucht. Dynamic causal modeling (DCM) hat gerichtete, effektive Konnektivität in Abhängigkeit der Cues getestet. Funktionelle (ungerichtete) Konnektivität wurde im sogenannten *resting state* untersucht. Dabei folgten die Probanden ihren eigenen Gedanken ohne externe Stimulation.

Im Rahmen der Dissertation haben vier Studien den Einfluss der *Cues* auf sozio-emotionale Prozesse erforscht. Im Fokus standen dabei diskrete Emotionen wie etwa Trauer und Freude sowie empathische Reaktionen in Bezug auf die Filmdarsteller. Außerdem wurde episodische Simulation untersucht. Diese beschreibt den Einfluss des Erinnerns an eigene Erlebnisse auf das Vermögen sich in die Filmdarsteller hinein zu versetzen. Zusätzlich wurde in einem Kommentar zu einer Emotionstheorie, der Quartet Theorie (QT), eine mögliche dysfunktionale Integration von *Cues* als Biomarker für Autismus, einer psychiatrischen Erkrankung mit Einschränkungen im sozialen und emotionalen Erleben, diskutiert.

Die erste Studie hat den modulierenden Einfluss von Musik untersucht und den Probanden Kusszenen aus Romantic Comedies entweder mit trauriger, fröhlicher oder ohne Musik präsentiert. Die zweite Studie hat nicht nur den modulatorischen Einfluss von Musik untersucht, sondern auch den eines narrativen Kontextes, der in Form kleiner Geschichten vor Empathieszenen präsentiert wurde. Empathieszenen haben einen Filmdarsteller in Frontalansicht in einer psychisch belastenden Situation gezeigt. Diese wurden mit oder ohne traurige Musik, und mit

oder ohne einen traurigen oder neutralen Kontext präsentiert. Der dritten Studie liegt der gleiche Versuchsaufbau zugrunde, nur wurde zusätzlich noch die Gehirnaktivität derselben Probanden im *resting state* gemessen. Ziel war es hierbei, die Konnektivität zweier Regionen zu untersuchen, die auf unterschiedliche Gedächtnistypen spezialisiert sind. Der Temporalpol (TP) ist für das semantische Gedächtnis (SM) spezialisiert und der Hippokampus (HP) für das autobiographische episodische Gedächtnis (AEM). Dabei wurde angenommen, dass sich die Konnektivität beider Regionen verändert wenn die Probanden episodisch simulieren, wofür die Integration beider Gedächtnistypen erforderlich ist. In Studie 3 wurde angenommen, dass episodische Simulation durch Kontext-Informationen ausgelöst wird.

Die ersten beiden Studien haben die Macht von Musik, Emotionen auszulösen, bekräftigt. Je nach Musik haben die Probanden die Kusszenen als signifikant fröhlicher oder trauriger erlebt. Musik hat ebenfalls dazu geführt, dass die Probanden signifikant stärkere Empathie für den Filmdarsteller empfunden haben. Auf neuronalem Level haben Konnektivitätsanalysen gezeigt, dass der anteriore superiore Gyrus (aSTG) multisensorische Informationen integriert und die Konnektivität vom Fusiformen Gyrus (FG) zu der Amygdala beeinflusst. Dieser Effekt war emotionsspezifisch, und zwar stärker bei den Kusszenen mit trauriger Musik als bei denen mit fröhlicher Musik.

Die Kontext-Informationen hatten auch in der zweiten Studie einen signifikanten Einfluss auf das Empathieempfinden der Probanden. Dieser Emotionseffekt war mit Aktivität im TP assoziiert, einer Gehirnregion, die semantische Informationen aus allen sensorischen Modalitäten integriert und eine wichtige Rolle für sozio-emotionales Verarbeiten spielt. Ausserdem hat der TP frühere Verarbeitungsstufen des ventralen visuellen Pfades, genauer im FG, top-down moduliert wenn Kontext-Informationen vor den Empathieclips präsentiert wurden. Dieser top-down Einfluss wurde durch Musik zusätzlich verstärkt.

Die dritte Studie hat gezeigt, dass Gehirnregionen, die auf unterschiedliche Gedächtnistypen spezialisiert sind (SM und AEM), während episodischer Simulation miteinander interagieren. Interhemisphärische Konnektivität vom linken aHP zum rechten TP wurde bei episodischer Simulation – sowohl während der Präsentation der Empathieszenen als auch während selbst induzierter Kognition (*resting state*) - übereinstimmend gefunden.

Die Ergebnisse der Studien wurden in einem vorläufigen Neurobiologischen Modell sozio-emotionaler Cue-Integration zusammengefasst. Das Modell beinhaltet mehrere neuronale Integrationsmechanismen, die durch die Dissertation belegt wurden. Es wurde gezeigt, dass convergence regions (aSTG und TP) multisensorische Informationen auf unterschiedlichen hierarchischen Levels integrieren und neuromodulatorischen Einfluss ausüben: Sie kontrollieren einerseits die Konnektivität zwischen zwei anderen Regionen, die in Emotionsverarbeitung involviert sind (FG und AMY) (gating effects) und top-down modulieren Verarbeitung im ventralen visuellen Pfad (FG). Dies ist in Einklang mit der Funktion des TP als semantischer Hub und *top-down facilitation models*. Darüber hinaus wurde eine laterale Spezialisierung von Gehirnregionen für unterschiedliche Gedächtnis-Subtypen gezeigt, was die Bedeutung interhemisphärischer Integration für komplexe soziale Kognition hervorhebt.

Zusammenfassend zeigt die vorliegende Dissertation den modulatorischen Einfluss sozio-emotionaler *Cues* auf die Emotionsverarbeitung einschließlich neuronaler Korrelate, die sich in Veränderungen von Netzwerkdynamiken ausdrücken. Sie unterstreicht die Kraft der Musik Emotionen auszulösen, spezifiziert die Rolle des Temporalpols in sozio-emotionaler Kognition und hebt die Bedeutung von Gedächtnisprozessen für soziale Prozesse hervor. Die gefundenen Integrationsmechanismen führen zu einem neurobiologischen Modell, das einen möglichen Erklärungsraum zum Verständnis neurokognitiver Integration darstellt. Das Modell eignet sich, zukünftige Forschungsfragen zu formulieren, insbesondere hinsichtlich psychiatrischer Störungen, die Beeinträchtigungen im sozialen und emotionalen Erleben und Verhalten zeigen, wie etwa Depressionen, Persönlichkeitsstörungen oder Schizophrenie. Möglicherweise können diese als Störungen neurokognitiver Integration mit dysfunktionalen Integrationsmechanismen verstanden werden.

Schlagwörter: Default Netzwerk, *dynamic causal modeling*, Emotion, Episodische Simulation, Film, Hippokampus, Gedächtnis, multisensorische Integration, Soziale Kognition, Temporalpol

List of original publications

Project 1

Pehrs C, Deserno L, Bakels JH, Schlochtermeyer LH, Kappelhoff H, Jacobs AM, Fritz T, Koelsch S, Kuchinke L. 2014. How music alters a kiss: superior temporal gyrus controls fusiform-amygdalar effective connectivity. *Soc Cogn Affect Neurosci.* 9:1770-1778.

Project 2

Pehrs C, Zaki J, Schlochtermeyer LH, Jacobs AM, Kuchinke L, Koelsch S (in revision). The temporal pole top-down modulates the ventral visual stream during social cognition. *Cereb Cortex.*

Project 3

Pehrs C, Schlochtermeyer LH, Kuchinke L, Koelsch S (submitted). Hippocampal-temporopolar connectivity contributes to episodic simulation during social cognition. *PLoS Biol.*

Project 4

Pehrs C, Samson AC, Gross JJ. 2015. The Quartet Theory: Implications for autism spectrum disorder. Comment on “The quartet theory of human emotions: An integrative and neurofunctional model” by S. Koelsch et al. *Phys Life Rev.* 13:77-79. doi: 10.1016/j.pprev.2015.04.025.

Additional publication¹

Manera V, Samson AC, Pehrs C, Ihno AL, Gross JJ. 2014. The eyes have it: The role of attention in cognitive reappraisal of social stimuli. *Emotion.* 14:833-839.

¹ This publication is also referred in the thesis.

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List of abbreviations

AEM	autobiographic episodic memory
aHP	anterior hippocampus
ASD	autism spectrum disorder
AMY	amygdala
aSTG	anterior superior temporal gyrus
aTL	anterior temporal lobe
BOLD	blood oxygen level dependent
BMS	bayesian model selection
CMS	cortical midline structures
DCM	dynamic causal modeling
DN	default network
EP	exceedance probability
FG	fusiform gyrus
fMRI	functional magnetic resonance imaging
FWE	family-wise error
HP	hippocampus
IFG	inferior frontal gyrus
LI	laterality index
mPFC	medial prefrontal cortex
MTG	middle temporal gyrus
MTL	medial temporal lobe
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
PFC	prefrontal cortex
PPI	psychophysiological interactions
QT	quartet theory
ROI	region of interest
RSFC	resting state functional connectivity

SD	semantic dementia
SM	semantic memory
SPM	statistical parametric mapping
TBEC	task based effective connectivity
TP	temporal pole
TPJ	temporoparietal junction

1. General introduction

1.1 Preface

Social functioning is a core component of real-life human experiences. High social functioning, as indicated by supportive and reliable social contacts to friends, colleagues or a partner, predicts social and psychological wellbeing and survival of the species (Couzin 2009; Adolphs 2010a). The human brain provides individuals with efficient tools to engage in interactions and cooperations, which enhance mutual chances for survival. These tools are e.g. language capabilities, social perception (e.g. biological motion, faces) and specifically the outstanding ability to engage in higher-order social cognition.

A key process is the ability to infer other people's mental state, which may be critical for adaptive social cognition. During social interactions, the brain integrates multisensory information (from the visual, auditory, olfactory, gustatory and tactile systems, Fig. 1) into a coherent representation and combines the input with social knowledge to evaluate the situation and to choose the appropriate behavior to engage in.

This dissertation project applies methods of functional and effective connectivity to functional magnetic resonance imaging (fMRI) data to examine the modulatory impact of different socio-emotional cues on neural network dynamics for multisensory integration and emotion processing. For this purpose, highly naturalistic stimuli were used, which had the capacity to parallel everyday social interactions, i.e. film clips. Movies combine dynamic visual with auditory stimuli and provide one of the closest representations of real life perception. According to Frijda (1989), movies are "illusions of reality". At the same time, movie clips are highly applicable to empirical research, because they are able to elicit intense emotions (Gross and Levenson 1995) and can be manipulated systematically for experimental purposes. The ability to engage with a fictitious movie character (Raz et al. 2014) additionally highlights the flexibility and complexity of human social cognition (Adolphs 2010a).

In the studies constituting this thesis, different movie clips were manipulated systematically with regard to visual, auditory and contextual information to examine their impact on neural network dynamics. Before the research questions and hypothesis are outlined in more detail, relevant neurocognitive integration theories are presented.

1.3 Neurocognitive integration theories

During social interactions, the perceptual input from the environment enters the human brain via multiple sensory modalities (Fig. 1). The processing of perceptual socio-emotional information (cues) starts in a bottom-up fashion in primary sensory, modality-specific cortices, continues over sensory association cortices to heteromodal areas and higher-order cognitive areas, while feedback projections moderate this process in a top-down fashion. This cascade is characterized by a progressive increase of complexity, which is an essential principle underlying the integration of perceptual information. A meaningful representation of the external world not only depends on external cues but importantly also relies on integration mechanisms. The internal integration of external cues follows mechanisms such as bottom-up and top-down processing, among others (Fig. 1). Those mechanisms are conceptualized in relevant neurocognitive integration theories and are described in the following section. In the General Discussion (5.), the findings of this thesis are linked to the theories resulting in a tentative neurobiological model of socio-emotional cue-integration (Fig. 17). Based on this model, outstanding future research questions are formulated (Table 3).

1.3.1 Theory of multiregional retroactivation

Damasio (1989) provided a theoretical framework for the understanding of memory and consciousness in the human brain. For the general binding problem of primary sensory information first processed separately in modality specific cortices, he provided the concept of local (at single modality cortices) and non-local (at higher-order association cortices or anterior temporal and frontal regions) convergence regions. The convergence regions operate on different hierarchical levels processing information on different stages of complexity (e.g. events or set of events) and are connected with recurrent interactions, feed-forward and feedback connectivity. Damasio (1989) accentuated the necessity of attention to coordinate these processes. The binding of single features in coherent entities can occur in unimodal sensory areas, but contextual complexity that is the arrangement of experiences in a situational stream of autobiographical events takes place in higher order convergence regions like the anterior temporal lobe (aTL). According to Damasio (1989), cognition occurs based on co-activated brain regions within large-scale brain networks containing multiple convergence zones that are reciprocally connected. For

memory retrieval, Damasio (1989) proposed the well-accepted principle of reinstatement (or “retroactivation”), according to which the same neural populations and connections during encoding of an original event (i.e. during memory formation) are reactivated at retrieval of the memory content.

Damasio’s theory (1989) provided the theoretical foundations for all main projects of this thesis (X). Advanced connectivity analyses were applied to fMRI data, suitable to investigate connectivity between brain regions, which is a core feature of his theory. According to Damasio (1989), convergence regions are interconnected, receive input from sensory modalities and are also connected to other functionally specialized brain regions. Furthermore, all connectivity analyses were applied to brain regions that are described as convergence regions in Damasio’s work (1989), i.e. the anterior superior temporal gyrus (aSTG) and temporal pole (TP). The projects support the concept of convergence regions in the human brain and provide important evidence for recurrent connections of convergence regions during integration of external socio-emotional cues.

1.3.2 Semantic hub theory

The semantic hub theory is another approach to resolve the binding problem of different modality specific information, with a focus on conceptual and semantic processing. Semantic memory (SM) (also called general knowledge) is defined as aspect of human memory that corresponds to general knowledge of objects, word meanings, facts and people, without connection to any particular time or place (Tulving 1972), namely knowledge that is developed through experience. Based on semantic dementia (SD), a neurodegenerative disease associated with progressive loss of semantic knowledge, McClelland and Rogers (2003; also Rogers 2004) developed the computational approach of a neural semantic hub. SD is associated with neurodegeneration of the aTL accompanied by deficits in recognizing objects across modalities. A gradual decline in domain general SM corresponds to the magnitude of tissue loss in aTL (Hodges et al. 1995). Consistently, Patterson et al. (2007) strongly emphasized the need of an amodal semantic operator for semantic processing in his so-called distributed-plus-hub view.

Hub accounts are in line with Damasio’s framework (1989) in the way that both frameworks account for specialized regions for binding of information. However, the difference to Damasio’s framework (1989) is that semantic hub accounts postulate only a single convergence region, the aTL, whereas Damasio’s framework

(1989) assumes multiple specialized convergence regions binding different pieces of information. According to Damasio (1989) convergence regions are not assumed to encode semantic representations themselves, but rather link different pieces of information in a highly interconnected network. In semantic hub accounts domain-general semantic representations are assumed as directly encoded in the aTL (McClelland and Rogers 2003; Patterson et al. 2007).

Next to evidences from semantic disorders (SD, stroke, Alzheimer's disease, Herpes simplex virus encephalitis), which intriguingly show that semantic deficits progressively increase with the extent of degeneration in the aTL (e.g. Lambon Ralph and Patterson 2008), there are supporting findings for the hub account in the neuroimaging literature (Devlin et al. 2002; Bright et al. 2004; Price et al. 2005; Rogers et al. 2006). To note, fMRI studies were not able to show the involvement of the TP in SM (Patterson et al. 2007; for a review see Wong and Gallate 2012), putatively because of susceptibility artifacts owing their proximity to air-filled sinuses to capture TP activation with fMRI (Devlin et al. 2000; Weiskopf et al. 2006; Visser et al. 2010a, 2010b; Binney et al. 2010). In line with these null findings, there are critical voices against the semantic hub theory (Olson et al. 2013). Olson et al. (2013) claim that studies on SD mostly used social stimuli and that semantic specificity was confounded with socialness. They further criticize that tissue loss in SD is not only restricted to TP and that sensory subdivision in TP would contradict the idea of a semantic hub.

The semantic hub account and the implication of the aTL in social and emotion processing are addressed in Study 2 of this thesis. Top-down modulations from TP as a convergence region and a semantic hub to lower level processing areas within the ventral visual stream were examined. It is also addressed in Study 3, where SM operations in TP and putative interactions with autobiographic episodic memory (AEM) (i.e. episodic simulation) were tested.

1.3.3 Top-down facilitation models

Top-down facilitation models aim to explain the binding problem with help of top-down cognitive control. They describe how higher-order cognitive areas for the processing of more complex, highly integrated information influence processing in lower level perceptual areas in a facilitating manner (Ullmann 1995; Bar 2003, 2006; Simmons and Barsalou 2003). They account for reciprocal connections between neuronal ensembles that process different levels of complexity and are thus in line

with Damasio's framework of convergence regions (1989) and semantic hub accounts (McClelland and Rogers 2003; Patterson et al. 2007).

Top-down facilitation models were developed based on findings from object recognition. When object recognition cannot easily be performed (e.g. because an image is blurred (low spatial frequency), earlier activation in higher-order areas develop initial guesses for possible object categories and back-project these guesses to lower level perceptual areas (Bar et al. 2003, 2006). Higher-order expectations and bottom-up perceptual information are integrated in an iterative manner with bi-directional connections until a match is found. Therewith, processing costs and processing time are decreased and object recognition facilitated. Hence, recognition relies on interactive higher-order cognitive and perceptual analysis. Based on animal studies, Bar (2003) assumed fast magnocellular pathways from primary visual areas to ventrolateral prefrontal cortex (PFC) to retrieve object-related knowledge, whereas expectations should be generated in orbital PFC (human analogue is inferior frontal gyrus (IFG)), while both regions are involved in top-down modulations (Bar 2003). Empirical evidence was provided by Bar et al. (2006) in a magnetoencephalography study where the orbitofrontal cortex (OFC) was activated 50ms earlier than signals of perceptual recognition in the fusiform gyrus and only when the presented object images comprised low spatial frequency components (blurred images). This indicates that top down-modulations from PFC exclusively occur when object recognition cannot be easily accomplished. This underlines the facilitating effect of top-down modulations for object recognition.

In Study 2, we used the concept of top-down facilitation models from object recognition as a model to describe top-down control during complex social cognition. We showed how top-down modulations increased as a function of task demands in line with findings from object recognition, while task demands in Study 2 referred to integration demands from multiple modalities. Project 4 discussed putative dysfunctional interactions of the orbitofrontal-centered with the hippocampus-centered affect system as described by the quartet theory (QT) (Koelsch et al. 2015) potentially resulting in impaired top-down modulations in autism spectrum disorder (ASD).

1.3.4 Integrative theory of cognitive control

A similar approach is provided by Miller and Cohen (2001) who highlighted feedback projection as a core mechanism of top-down executive control. Their framework

states that the PFC is involved in mapping perceptual inputs with internal states or intentions (thoughts, emotions, memories) and controls behavioral outputs of complex human coordination and behavior. Thereby the PFC modulates brain-wide neural activations in systems like sensory modalities, emotional evaluation, memory retrieval, etc. and is therefore the central operator to guide and coordinate cognition in the human brain, especially when the input is ambiguous proposing several behavioral alternatives. In this case, cognitive control is required to choose between alternatives and to perform the contextually most appropriate response. When behaviors have proven successful, reinforcements signals strengthen the responsible neural connections for future actions enabling learning and diminishing the need of PFC control in future scenarios. Consistent with top-down facilitation models, they assume that the PFC exerts more influence with stronger demand for cognitive control.

Miller and Cohen (2001) listed criteria, which are required for a region to exert top-down control. These are a high capacity for multimodality or convergence (input from multiple sensory systems) and integration (connections to cortical and subcortical motor systems, limbic and midbrain structures involved in affect, memory and reward). They presented the anatomical structure and connections of PFC as suitable to match these criteria, but stressed that other brain areas might fulfill these criteria as well. The TP is another candidate region fulfilling those criteria. Indeed, the TP was found to exert top-down modulations as we will learn in Study 2. The concept of convergence regions, semantic hub accounts and top-down models are combined in suggesting the TP as a region to exert top-down influence.

1.3.5 Episodic simulation

All neurocognitive integration theories refer to memory processes as an essential constituent of external cue-integration² (Fig. 1). Before I focus on episodic simulation, which was the focus of Study 3, I want to describe in brief the links of neurocognitive integration theories to memory functions.

² Edelman (2001) intriguingly describes how conscious representations are memory related at all times by linking the processing of sensory information with internal constructive processes. According to Edelman (2001) cortical circuits carry out ongoing perceptual categorization from conceptual memory, such that perception is a stream of continuous correlated value-categorizations resulting in a “remembered present”.

In his framework for multiregional retroactivation, Damasio (1989) accentuated that every perceptual experience is related to memory processes. When a rose is identified as rose, conceptual knowledge stored in SM is accessed and gets activated as an associated (multisensory) image. In his theory, the convergence regions in the association cortices integrate multisensory information and reactivate the anatomical locations where the associated internal images or representations (e.g. roses) are stored to send those as top-down signals to early sensory cortices (see also Meyer 2012). The recalled associated images are internal activations of experience-based representations and thus perception-independent. It is important to bear in mind that Damasio's framework (1989) assumes recurrent interactions between convergence regions at different orders (hierarchical levels of abstraction), memory processes however are thought to exert influence only over feedback signals (i.e. 'reactivation mechanism'). According to Damasio (1989), different domains of memory processing (e.g. episodic, procedural, declarative) are processed in dissociable structures of the brain accounting for the varieties of amnesias depending on the anatomical localization of the brain lesions.

Top-down facilitation models directly address these mechanisms by showing how internal construction can facilitate object recognition in lower level perceptual areas (the moment assuming the image to be a rose). The initial guesses, which are iteratively adjusted to the perceptual input, are constantly retrieved from conceptual knowledge, emphasizing SM retrieval as central part of top-down facilitation (Bar 2003).

Consistently, the semantic hub theory as presented by McClelland and Rogers (2003) implies that multisensory information is integrated in the hub (located in anterior temporal areas) where it is conceptualized by SM. The knowledge, however, is assumed to be stored in patterns of connection strengths between brain areas gradually acquired through experience (developmental learning) and not reflected by brain regions, which are specifically involved in memory processing. Patterson's formulation of the distributed plus hub view (2007) is more radical in the sense that it assumes the SM retrieval taking place not by connection weights but instead solely in the hub.

Miller and Cohen's framework for top-down cognitive control (2001) states that the PFC is responsible for memory retrieval when sensory input demands an appropriate behavior and differentiates feedback signals to intermediate systems (for short-term or working memory) but also suggests that PFC guides retrieval from

long-term memory. However they assume another cognitive control system in the hippocampus (HP), next to the PFC-control system, which stores episodic memory. They describe interactions between these two systems such that the HP is involved in long-term memory, whereas the PFC rather detects regularities between episodes (Miller and Cohen 2001).

Episodic simulation describes the process that experiences from one's past are used as source to simulate events (Schacter et al. 2012). The simulation process can refer to future as well as to present events and is based on interactions of semantic and episodic memory (Szpunar et al. 2014).

As described above, SM is general knowledge, independent of the specific episode when that knowledge was acquired (Tulving 1972). AEM refers to personal events, which are related to a specific time period in the individual past, embedded in a spatial context and bear the potential to be vividly re-experienced with details and emotions (Tulving 2002; Moscovitch et al. 2006).

In a social context, episodic simulation refers to the use of previous experiences for mentalizing, i.e. the drawing of inferences on the mental state of another person (Goldman 2006; see 1.4.1). Correspondingly, the episodic simulation hypothesis states that people use own experiences to simulate others' thoughts and feelings (Ciaramelli et al. 2013; Mitchell et al. 2006a; Yang et al. 2013) and can increase prosocial orientation by improving the ability of perspective taking (Gaesser and Schacter 2014). Consistently, memory processes are increasingly addressed in research on socio-emotional cognition (Spreng 2013) (see 5.5). Episodic simulation takes place during both internally (self-generated) (Cansino et al. 2002; Yonelinas et al. 2005; Kim and Cabeza 2007; Schacter et al. 2012) and externally driven cognition (Dolan 2000; Perry et al. 2011).

In Study 3, we sought to map the integration of SM with AEM onto the connectivity of two brain regions, which are key for AEM and SM, the anterior hippocampus (aHP) and the TP. This is done during internally (rest) and externally (task) driven episodic simulation. In Project 4, putative dysfunctional mnemonic integration is discussed in ASD with regard to impaired top-down control.

1.3.6 Internal mentation

Neurocognitive integration can be dissociated in two sub-systems that switch and interact (fluctuate) regularly during everyday experiences (Binder et al. 1999; Smallwood et al. 2008). These are the external mode of cognition, in which the

attention is mainly focused on the external world (Fig. 1, above dashed line) and the internal mode of cognition, in which the attention is mainly focused on the internal world (Fig. 1, below dashed line).

The neural network primarily associated with an internal processing is the so-called default network (DN) derived from studies on 'resting state' (correlations between low-frequency blood oxygen level dependent (BOLD) signal changes observed in the absence of a structured task, Biswal 1995; Shulman et al. 1997; Gusnard et al. 2001a; Raichle et al. 2001; Greicius et al. 2003), whereas it is typically inversely correlated with a task (Raichle et al. 2001). The network represents the "stream of thought", as described by James (1890) or internal mentation (Andrews-Hanna 2012). Using graph analysis, Andrews-Hanna et al. partitioned the DN in subnetworks, which are controlled and linked by hubs, located in the cortical midline structures (CMS) (Andrews-Hanna et al. 2010). The dorso medial prefrontal cortex (dmPFC)-subsystem is implicated in mentalizing, moral decision making, social narrative comprehension, social reasoning and conceptual processing, whereas the medial temporal lobe (MTL)-subsystem is implicated in episodic memory, episodic future thinking, retrieval of contextual/semantic processing, imagination and navigation (Andrews-Hanna 2012).

Since the beginning of studies on resting state in the early 90s, an upcoming line of research aims to specify the quality, form and frequency of mental operations during rest. Several post-scanning questionnaires were developed to investigate an individual's experiences in terms of content and form (images vs. words), i.e. the New York Cognition Questionnaire (Gorgolewski et al. 2014), the Amsterdam Resting-State Questionnaire (Diaz et al. 2013), the Dundee Stress State Questionnaires (Matthews et al. 1999) and the Resting State Questionnaire (Delamillieure et al. 2010). Because of their retrospective nature, these measures might bear the problem of memory-biases. Another approach uses an online method called experience sampling. The technique is to gather thought probes by periodically interrupting people and asking questions about their mental activity (O'Callaghan et al. 2015; Stawarczyk et al. 2011).

Overall, experience sampling and questionnaires have shown that during rest, people engage in self-referential mentation about imagining/planning the future, inferring mental states of others' current concerns or reflecting about social interactions (Andrew-Hanna et al. 2010; Fox et al. 2013; Gorgolewski et al. 2014), i.e. mental activities that can be allocated to social cognition, self-reflection, internal

processing and episodic simulation (1.4).

In Study 3, brain activity was measured during resting state and task state in the same set of participants, using fMRI. This allowed us to directly compare brain organization during two functional states (rest and task) (see discussion 5.6).

1.4 Socio-emotional cognition

The present thesis examines neurocognitive integration specifically in socio-emotional cognition. Dunbar's social brain hypothesis (1993, 1998) links the volume of the neocortex to social cognition abilities to propose the complexity of social cognition as a unique feature of the human species (Adolphs 2009). Even though there are contradicting evidences (e.g. Azevedo et al. 2009), the hypothesis can still be used to describe the complexity of human social cognition. Before the relevant brain areas are reviewed, mentalizing is discussed in more detail. This is due to the fact that in the literature, mentalizing and social cognition are used synonymously and that they are the main cognitive processes investigated in this thesis.

1.4.1 Mentalizing

Mentalizing (theory of mind) describes the implicit (automatic) or explicit (with awareness) attribution of mental states to others (desires, beliefs) in order to explain and predict their behavior (Frith and Frith 2012). Implicit mentalizing abilities are developed in early childhood and can be reliably observed at age of 1.5 years, whereas explicit mentalizing can be observed between the ages of 4 and 6 years (Frith and Frith 2003). Mental illnesses characterized by social dysfunctional behaviors like ASD, sociopathy, borderline personality disorder, schizophrenia, depression, etc. show deficits in the temporal trajectory of gaining mentalizing abilities (Adolphs 2010a). Mentalizing is demanded in various social contexts and shows strong conceptual overlap with other related constructs like empathy (emotional and cognitive), compassion, emotional contagion, sympathy; to only list a few (for reviews see Walter 2012; Zaki and Ochsner 2012).

In this dissertation thesis, compassion is specifically examined in Study 2, which is defined as a prosocial subaspect of empathy (Zaki and Ochsner 2012), the feeling for someone suffering and the desire to help (Goetz et al. 2010). The question whether other species have mentalizing capabilities was raised in the late 70s by Premack and Woodruff (1978) and can nowadays partly be affirmed (Clayton et al.

2007; Silk 2007; Call and Tomasello 2008). However, it is described as different from human social cognition (only implicit) and non-human primates are thought to lack the ability to understand false beliefs (Call and Tomasello 2008). Some studies were not able to show prosocial behavior in non-human primates (Silk et al. 2007; Vonk et al. 2008), whereas others did (de Waal 2008; Liebal et al. 2014). However, there is no doubt that the complexity of social cognition in the human species is superior to other species (Call and Tomasello 2008).

Mentalizing was examined in many disciplines, using multiple sorts of tasks. Most prominently is the false belief task, which is successfully accomplished when explicitly knowing that another person holds a false belief and which is often used to examine the development of mentalizing abilities in children presenting little short stories in form of vignettes or cartoons (Wimmer and Perner 1983; Amodio and Frith 2006; Saxe 2006). Other explicit tasks are animations of geometric shapes (Castelli et al. 2000), man made vs. computer music (Steinbeis and Koelsch 2009) and economic games (prisoner's dilemma or trust games; Tabibnia and Lieberman 2007; Hampton et al. 2008; Coricelli and Nagel 2009; Yoshida et al. 2010).

However, the application of mentalizing abilities in real life is rather automatic, complex and dynamic, requiring naturalistic (multisensory) stimulus material in combination with behavioral measures (Zaki and Ochsner 2009, 2012). This was accomplished in the present thesis.

On the basis of neurocognitive integration theories, it is important to consider the modularity of the human brain to process social perceptual input (faces, bodies, odor; for a review see Adolphs 2010a) and how this input is used to infer mental states of conspecifics.³ One approach to investigate this question is provided by the framework of cue-integration (Zaki 2013), which states that mentalizing relies on Bayesian conditional probabilities of cues to predict targets' mental states (see 1.4.3). Accordingly, systematic changes of cue configuration can operationalize cue-dependent impact on neural network dynamics.

1.4.2 The neural network for social cognition

Since the 90s there is considerable amount of meta-analysis and review articles

³ A publication by Manera et al. (2014) using stimulus material from this dissertation project in combination with eye tracking has shown that participants make use of the emotional regions of the face (mouth, eyes) to increase or decrease their compassion. The experienced negative emotions of the participants are mediated by the time spend on the emotional regions of the face.

about the domain specificity of the brain for social cognition. Which brain regions constitute *The Social brain*⁴ is largely dependent on the task, like the perception of social vs. non-social stimuli (e.g. (emotional) faces vs. tools, body movement perception (point light task)), mentalizing tasks (false belief task, inferences on geometric shapes, observation of a spouse getting electro shocks) or economic games (e.g. cooperative and trust games).

In her review, Brothers (1990) proposed an initial set of structures for social behavior, namely the amygdala (AMY), the OFC, and the TP's. Frith and Frith (2003) focused on mentalizing and found three regions to be consistently activated during implicit and explicit mentalizing⁵: the medial prefrontal cortex (mPFC), the TPs and the posterior superior temporal sulci. In a popular meta-analysis based on 200 fMRI studies, van Overwalle (2009) highlighted two regions to be mainly involved in social cognition, which are the mPFC and the temporoparietal junction (TPJ) in line with Saxe and Powell (2006), who list the posterior cingulate cortex (PCC) as well. Mar (2011a) found the orbital part of the IFG using story based mentalizing tasks and is thought to be part of the human mirror neuron system (Iacoboni et al. 1999; Rizzolatti and Craighero 2004). Specific functional specializations of the regions within in the mentalizing network are discussed. The mPFC for example is thought to be particularly involved in mental compared to physical processing on a more abstract cognitive level (Frith and Frith 2003; van Overwalle 2009). The TPJ is thought to be particularly involved in mental state inferences on a rather perceptual level but also for processing of agency and attentional reorienting (Saxe and Powell 2006; Decety et al., 2007; Mitchell et al. 2008a; van Overwalle 2009). The TP is assumed to retrieve social knowledge in form of scripts (Frith and Frith 2003) and is specifically involved in social and emotional processing (Ochsner and Lieberman 2001; Cacioppo et al. 2007; Ochsner 2007; Olson et al. 2007, 2013; Lieberman 2007; Mitchell 2008b; Adolphs 2009, 2010a; Frith and Frith 2012).

There is an astonishing overlap between the social cognition network and the DN (Spreng 2009), which was already introduced above as a key network engaged during internal mentation (1.3.6). The DN is discussed to be particularly social (Mitchell 2006b; Schilbach et al. 2008; Mars et al. 2012). Core nodes of the DN are the PFC and PCC (i.e. CMS) and the TPJ (Mars et al. 2012). The HP, the MTL, the

⁴ The existence of an ultimate 'social brain' still needs to be proven.

⁵ The term mentalizing network is often used interchangeably with a 'social cognition network' or 'social brain'.

lateral temporal cortex and the TP are described as the extended DN (Greicius et al. 2004; Mars et al. 2012). A recent study demonstrated a parametric increase with social but not cognitive working memory load (Meyer et al. 2012). In congruence, the group size in which monkeys were housed predicted functional connectivity and changes in grey matter volume of DN regions (Sallet et al. 2011). The CMS are involved in the processing of self-referential information (Northoff et al. 2006; Gusnard et al. 2001b) and are critical for inferring mental states of oneself and others (Uddin et al. 2007).

1.4.3 A framework for cue-integration

In his framework for cue-integration, Zaki (2013) related complex social cognition to physical perception and suggested that inferences on an other's mental state resembles integration processes during multimodal physical perception and can thus provide the basis for the development of formal Bayesian models for social cognition. Internal constructive integration processes (in opposition to objective perception) applies likewise to physical and social cues. Conditional probabilities of conflicting or converging cues (the probability of one cue to occur with another, e.g. tears to occur with sobbing) are integrated with the perceivers' experience and learning history, such that usually the probability of a person being sad is high when tears and the sobbing occur. Multiple cognitive processes are used for inferences (mentalizing, experience sharing etc.). According to Zaki (2013), these models can help explaining a change of probabilities over time, social inferential accuracy and biases and disordered cue-integration in psychiatric disorders.

1.5 Synthesis

This thesis uses relevant neurocognitive integration theories to elucidate the neural underpinnings for integration of socio-emotional cues leading to an individual ('social') experience (Fig. 1).

Socio-emotional cues from an external world (Fig. 1, above dashed line) are integrated in the human brain by neural mechanisms, which are derived here from neurocognitive integration theories. Those are, on an abstract level, convergence regions, semantic hub accounts, top-down processing (top-down facilitation models, PFC cognitive control) and Bayesian models of cue-integration. They are related to memory processes (e.g. episodic simulation) and can be assumed to be active

during both externally driven and internally driven cognition, while the latter is cognition under absence or scarcity of external socio-emotional cues. On a more concrete level, brain mechanisms are modality specific cortices (initiating a bottom-up processing), functionally specialized brain regions (e.g. TP for socio-emotional processing), the activity of brain networks on a nano-, micro-, meso- and macro-scale and integration and coordination of activity from two hemispheres including lateral specialization. These mechanisms (Fig. 1) build the theoretical framework for the four studies. The mechanisms will be linked and clarified by the findings of this thesis in order to come closer to a neurobiological model of socio-emotional cue-integration (Fig. 17).

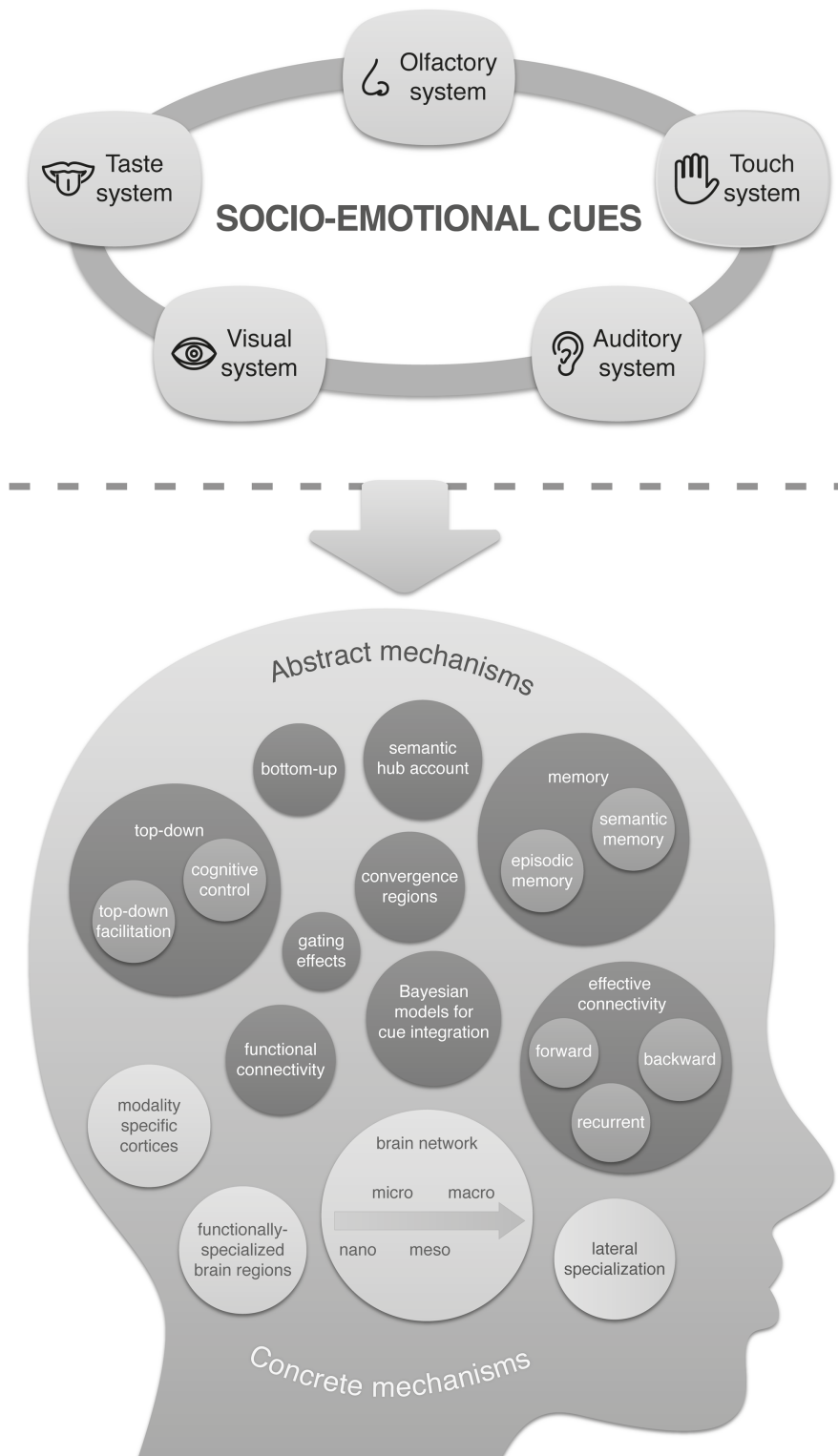


Figure 1 Neurocognitive integration mechanisms.

Based on neurocognitive integration theories (1.3), general mechanisms for the integration of socio-emotional cues (on top) are listed along a gradient from a more abstract theoretical level (towards the top of the skull) to a more concrete level (towards the neck). The findings of this thesis will link and specify the mechanisms resulting in a neurobiological model of socio-emotional cue-integration (Fig. 17). The dashed line separates the 'external' from the 'internal' world.

2. Research questions and hypotheses

The overall aim of this dissertation is to advance the understanding of integration processes in the human brain during social cognition. More specifically, how multimodal socio-emotional input is integrated into a meaningful representation and affects emotion processing. This goal is pursued by stratifying naturalistic stimuli (film clips) in modality specific components. Systematic variations of cue combinations (visual, auditory, contextual) allowed the dissociation of cue dependent impact on experienced emotions and underlying network dynamics.

This general research question can be partitioned in five sub-questions. The first question addresses the integration of visual and auditory cues (Project 1 and Project 2).

The second question addresses the integration of visual, auditory and contextual information (Project 2) and thus centers more on memory-based internal construction than the first question.

The third question addresses episodic simulation, which is the use of autobiographic experiences to understand current events or future scenarios and mental states of other persons (Project 3).

The fourth question centers on differences in brain organization during two functional states, in which the subjects were being scanned, i.e. internally vs. externally driven cognition (Project 3).

The fifth question relates to putative impairments in cue-integration in mental disorders that are characterized by aberrant socio-emotional functioning, such as autism spectrum disorder (ASD) (Project 4). In the following sections, the five research questions are described in more detail.

2.1 Integration of visual and auditory cues

Movie clips and music are highly suitable to elicit strong emotions (Gross and Levenson 1995; Koelsch 2013a). In combination with film, the music is used from spectators as a valuable source of emotional information (Cohen 2001; Kuchinke et al. 2013). By integrating visual and auditory information, film parallels important aspects of everyday emotional experiences and provides a naturalistic environment to study social cognition.

The first question relates to the modulatory impact of emotional music and was addressed in Study 1 and Study 2. In the first project, kissing scenes of romantic

comedies were presented either with happy music, with sad music or without music during functional magnetic resonance imaging (fMRI) scanning (Fig. 2). After presentation of each kissing scene, the participants gave information about their emotional reaction in terms of valence, arousal, happiness and sadness ratings. In the second project, empathic film clips (Plantinga 1999) depicted 12s long and close-ups of a sad human face and were presented either with emotion congruent (sad) music or without music and either with a sad, a neutral or without a contextual framing (see 2.2). After each film clip, the participants rated their emotional experience in terms of being moved and compassion (Fig. 6). In both studies, we expected the music to increase the experienced emotion consistent to the emotional quality of the music (e.g. to feel more sad/happy in dependence of the music). In Study 2, we expected increases of empathic concern for the movie characters due to the music.

Neural correlates were expected in a brain network for multisensory integration of emotion and social cognition. In line with Damasio's multiregional retroactivation theory (Damasio 1989) (1.3.1), we expected that visual and auditory activations would be integrated in the so called convergence regions, which in turn would have neuromodulatory impact on brain circuits involved in emotion processing. Neuromodulatory impact describes the influence of activity in one region on the activity of another region or the connectivity between two other brain regions (i.e. gating effects). We also expected the music to increase the integration demands in the human brain due to an increase of perceptual and semantic information from multiple modalities. An increase of integration demands might be accompanied by potential top-down modulations of perceptual processing streams consistent with top-down facilitation models (1.3.3).

2.2 Integration of visual, auditory and contextual cues

Another source of emotional information in film is the narrative context in which the characters are embedded. The story provides the relevant background information for the spectators to draw inferences on the mental and emotional state of the characters. It enables the spectators to follow them through the story, to put themselves into their shoes and sometimes to identify with the characters. Consistently, sharing the emotional experience with a movie character is according to Raz et al. (2014) a core mechanism for emotion elicitation in movies. In social neuroscience, these processes can be used to examine effects of contextual framing

on perceptual input and emotion processing.

This was done in Study 2. Next to the modulatory impact of emotional music (2.1), we asked how different contextual framings (sad and neutral contexts) influence the emotional reaction of the participants. We expected that a sad context would increase the empathic concern for the movie characters. On a neural level, we expected these processes to be associated with BOLD responses in the ventral meaning pathway spreading from primary visual areas along the ventral and lateral temporal lobe pointing to TP, and inferior frontal gyrus (IFG) as well as prefrontal areas. Following the semantic hub theory and Damasio's theory of convergence regions (1989), we expected particular BOLD response in the TP, which might be enhanced for sad compared to neutral contextual framings due to its involvement in emotion processing (Olson et al. 2007; Gainotti et al. 2015). Based on top-down facilitation models (Bar et al. 2003, 2006) and results from object recognition (Tyler et al. 2004; Chan et al. 2011; Yvert et al. 2013), we assumed top-down modulations from TP downstream the ventral pathway as a function of contexts and music.

2.3 Episodic simulation

In Study 2, a parametric analysis revealed that the right TP and bilateral anterior hippocampi tracked participants' experience of compassion (see 4.3). This finding was discussed in relation to the episodic simulation hypothesis, which describes the use of autobiographic experiences to infer another person's mental state (Mitchell et al. 2006b; Perry et al. 2011; Ciaramelli et al. 2013). It is important to note that we assumed the context information to trigger the retrieval of autobiographic memory based on studies showing how processing of a story is related to retrieval of emotional autobiographic memories (Mar et al. 2011b). Episodic simulation requires the integration of context-dependent AEM with context-independent semantic memory (SM) (general knowledge). The left anterior hippocampus (aHP) is key to AEM (Maguire 2001; Moscovitch et al. 2006) and the right temporal pole (TP) is key to (emotional) SM (Rogers et al. 2006; Olson et al. 2007; Binney et al. 2010).

In Study 3, we mapped the episodic simulation onto changes of the connectivity between these two key regions as a function of AEM integration and expected coupling-changes between left aHP and right TP when a context was presented prior to the film clips. Since memory processes are not only involved in social cognition during tasks but also crucially implicated in cognitive processes during rest (Binder et al. 1999; Schacter et al. 2012) (see 1.3.6), we applied

connectivity analyses to both internally (rest) and externally (task) driven cognition. Cole et al. (2014) have compared functional connectivity during rest and multiple tasks (social, emotional, n-back, motor etc.) and revealed striking overlap of network activity irrespective of task. Consistently, we expected a strong correspondence between intrinsic and extrinsic connectivity.

2.4 Internally vs. externally driven cognition

As described in the Introduction section (1.3.6), human cognition can be divided in two sub-systems that switch and interact in a regular flow of everyday experiences (Smallwood et al. 2008; Dixon et al. 2014): An internally driven state, in which the attention is focused aberrantly from the external world, and an externally driven state, in which the attention is focused on the external world (on external cues, Fig. 17).

In study 3, we expected similar results for TP-aHP connectivity analyses based on demonstrations that the same intrinsic brain architecture underlies and shapes extrinsic neural connectivity (Cole et al. 2014). In addition, episodic simulation takes place during internally and externally driven cognition (Buckner et al. 2008; Christoff et al. 2009; Spreng and Grady 2010a; Andrews-Hanna et al. 2010, 2014), which is why we assumed a similar TP-HP connectivity profile during internally and externally driven cognition.

2.5 Impaired cue-integration in autism spectrum disorder

The fifth question discussed putative impairments of cue-integration in ASD. It was addressed in a comment on “The Quartet Theory of Human Emotions: an integrative neurofunctional model” by Koelsch et al. (2015). The theory states that emotion percepts are generated in the brain by the interaction of 4 systems, each responsible for a different class of emotions. (1) The Brainstem-centered affect system is responsible for the vegetative system like for example the sleep/wake cycle. (2) The Diencephalon-centered affect system is related to satisfaction of bodily need states. (3) The Hippocampus-centered affect system is mostly associated with attachment-related emotions. (4) Finally, the orbitofrontal-centered affect system is responsible for the evaluation of internal and external cues. All affect-systems interact with another but also with the so-called effector systems (biological systems like for example motor systems).

ASD is a neurodevelopmental disorder characterized by social and

communication deficits as well as restricted and repetitive behaviors (American Psychiatric Association 2000). Specific deficits include failure to initiate reciprocal social interactions, verbal and non-verbal communication difficulties, decreased sensitivity to social and emotional cues and limited perspective-taking abilities. Therefore it seems almost provocative for research on ASD that according to the QT, the hippocampal system is responsible for attachment-related emotions. We postulated a dysfunctional interaction of the hippocampal with the orbitofrontal system and discussed this hypothesis based on behavioral and neural evidences that are related to problematic patterns of emotion reactivity in ASD.

3. General methodology

The general methodology describes the experimental approach of measuring functional magnetic resonance imaging (fMRI) activity while participants passively followed naturalistic film clips and the application of (functional and effective) connectivity analysis to fMRI data.

3.1 Passive viewing paradigms

“Just because it’s fake doesn’t mean I don’t feel it.”

Laird in the TV series ‘Girls’, Season 3, Episode 4

Naturalistic stimulus material has numerous advantages compared to static stimulus material like e.g. the common set of photographs of the IAPS (International Affective Picture System (IAPS), Lang et al. 2005). Film stimuli are emotionally intense, cognitively complex (dynamic, multimodal and reliant on meaningful narrative), high in attentional capture and ecologically valid (Gross and Levenson 1995). Therefore, film is increasingly used in complex social neuroscience (Levesque 2003; Hasson et al. 2004; Goldin et al. 2005; Eldar et al. 2007; Spunt and Lieberman 2012). Several stimulus sets taken from complex movies have been developed with the aim to induce emotional responses in experimental settings (Gross and Levenson 1995; Hagemann et al. 1999; Schaefer et al. 2010). This meets the claim of Zaki and Ochsner (2009) to apply naturalistic stimuli in social neuroscience. According to them, information during social interactions in real-life is multimodal (visual, semantic and prosodic), dynamic (serial integration over time) and contextually embedded.

Film stimuli hold these characteristics and at the same offer the possibility for a high level of experimental control. The studies of this dissertation thesis use these advantages. In all studies, film stimuli were presented in a passive viewing condition to participants in the MRI scanner. The participants were instructed to solely watch the movies without a specific task at hand. This was done to better mirror real life perception, in which perceivers don’t have to perform a distracting task like explicit judgments about mental states or feelings. We wanted the participants to be able to engage unrestrained in emotional and cognitive reactions and asked for ratings of experienced emotions after the film clips (see Mauss and Robinson, 2009). This further has the advantage to avoid movement during presentation of the movies, which has influence on neural patterns, making it difficult to interpret fMRI results.

Self-statements were acquired on selected emotion dimensions in the scanner using a trackball to move a cursor on 7-point Likert scales. Standardization of the film stimuli was reached by using short film clips matched by type of scene (kissing scenes depicting two people) or empathic film clips, which were even more standardized by a fixed length (12s) and consistent visual information, i.e. a close up of a sad human face.

Movies are generally accompanied by music and spectators use the soundtrack as a source of emotional information (Kuchinke et al. 2013). Music has a strong capacity to elicit emotions (Blood and Zatorre 2001; Koelsch 2013a), to modulate emotion processing of dynamic visual stimuli (Eldar et al. 2007; Pehrs et al. 2014) and to trigger mentalizing processes (Steinbeis and Koelsch 2009; Parsons et al. 2014). Movies in combination with emotional music parallel naturalistic perception even to a bigger extent than movies alone and thus better meet the claim of Zaki and Ochsner (2009) to apply naturalistic stimuli in experimental settings.

Since dynamic audiovisual clips consist of longer time epochs with cognitive and emotional processing unfolding over time, new technical analysis like independent component analysis (Bartels and Zeki 2005; Wolf et al. 2010), intersubject correlations (Hasson et al. 2004, 2008; Jääskeläinen et al. 2011; Nummenmaa et al. 2012), network cohesion index (Raz et al. 2014) (see also the promising eigenvector centrality mapping; Lohmann et al. 2010; Koelsch et al. 2013b) were applied. To the best of my knowledge, the studies of this thesis are the first to combine film stimuli with dynamic causal modeling (DCM) to infer effective connectivity within brain networks during multisensory social cognition.

3.2 Tasked based effective connectivity

“Essentially, all models are wrong, but some are useful.”

George E. P. Box & Norman R. Draper, 1987

DCM is a Bayesian approach to infer changes of effective connectivity from different measurement techniques (e.g. fMRI, electroencephalography or magnetoencephalography) implemented in the statistical parametric mapping (SPM) analyses package (Wellcome Department of Cognitive Neurology, London). The overall approach is to model different connectivity profiles and to test which model best fits the measured data such that inferences can be drawn on dynamics of brain networks. Functional connectivity analysis allows conclusions as to which areas a

region of interest (ROI) is connected to or to which areas of the brain a ROI is connected to during one condition compared to another, i.e. psychophysiological interactions (also labeled ‘weak model of effective connectivity’; Friston et al. 1997; Gitelman et al. 2003). The difference and advantage of DCM compared to these techniques is the possibility to infer changes of effective connectivity, namely how activity in one brain region changes the activity in another. This allows an attribution of directionality (see also structural equation modeling, McIntosh and Gonzalez-Lima 1994; Büchel and Friston 1997, and multivariate autoregressive models, Harrison et al. 2003).

DCM analysis consists of three steps: model specification, model estimation and model selection. In the DCM framework, regional time-series based on a previous general linear model analysis are used to analyze connectivity and especially its modulation by experimental conditions (B matrix). DCM treats the brain as a dynamic input-state-output system. The inputs are the experimental manipulations, the state variables are neuronal activities and the outputs are the regional hemodynamic responses measured with fMRI. With the knowing of inputs and outputs, changes in the hidden neuronal dynamics can be modeled to examine the influence that one neuronal system exerts over another (Friston et al. 2003). This is expressed by the following bilinear state equation:

$$\dot{z} = Az + \sum_{j=1}^m u_j B_j z + Cu$$

[1]⁶

Bilinear DCM allows modeling of three parameters: endogenous coupling (A matrix) between two regions (“intrinsic connections”); (2) direct extrinsic input of specific regions (“driving inputs”, C matrix) and most importantly (3) context-specific coupling accounting for the effects of experimentally controlled network perturbations (“modulatory input”, B matrix). This bilinear state equation was extended by a nonlinear term (D matrix) to describe the influence of a region on the coupling of two other brain regions (Stephan et al. 2008). A nonlinear DCM was applied in two studies of this thesis, enabling second order inferences on interactions between

⁶ \dot{z} is the change of a neural state vector over time ($\dot{z} = \frac{dz}{dt}$; state variables are neural firing rates), u are the external inputs, which can be modulatory or driving.

synaptic inputs.

$$\dot{z} = Az + \sum_{i=1}^m u_i B_i z + \sum_{j=1}^n x_j D_j z + Cu$$

[2]

In DCM for fMRI, the modeled neuronal dynamics are transformed into a hemodynamic response by using a hemodynamic forward model, which translates neuronal states into predicted measurements allowing access to the ‘hidden state’, the actual neural level (Friston et al. 2000; Stephan et al. 2007). The parameters are iteratively estimated minimizing the difference on the neural and hemodynamic level in a Bayesian framework as described by Friston et al. (2003). Applying classical statistic inferences on parameters, which are measured in Hz (exponential nature of partial differential equations), can give information about the size and nature (inhibitory, excitatory) of effects.

Bayesian model selection (BMS) is an approach to compare model evidences for detection of the winning model, which best explains the data. BMS takes the fit of the models into account, primarily based on the number of free parameters in relation to the model complexity. With higher complexity, the relative fit of a model may increase but generalizability may be reduced. For BMS, we used a novel random-effects approach at the group level, which deals gracefully with outliers (Stephan et al. 2009). Random-effects BMS gives so-called exceedance probabilities (EP), the probability that one model is more likely than another. We furthermore applied BMS on family levels to identify families of models, which are more likely than others (Penny et al. 2010). DCM was applied in Study 1, Study 2 and Study 3.

3.3 Resting state functional connectivity

In experimental studies, resting state describes the state in which participants are scanned in the absence of a cognitive task, specifically in fMRI studies the time in the scanner between task blocks or before or after task (eyes open or eyes closed). Rather randomly a network was found that was activated peculiarly during these periods and additionally anti-correlated with the dorsal attention network (Shulman et al. 1997; Raichle et al. 2001; Fox et al. 2005). Later it was found that the activity is not so ‘default’ as its name might suggest but instead highly engaged in mind

wandering and mental inferences of present, past and future as well as self and other related thoughts (see 1.3.6, 1.4.2 and 2.4). Resting state functional connectivity (RSFC) is based on correlations of spontaneous low-frequency fluctuations. Since during these periods there are no conditions which can be contrasted against each other (for regressing out the noise), the physiological noise (scanner artifacts, motion, cardiac and respiratory cycles) bears a specific challenge for data analysis, because it contaminates low-frequency fluctuations of blood oxygen level dependent (BOLD) signal when performing seed based functional connectivity analysis (Cordes et al. 2001; Shmueli et al. 2007). Therefore, time-series are usually cleaned before analysis (smoothed, filtered for low-frequency spectrum (0.01-0.08 Hz) etc.), which follows a simple procedure: a seed time-series is extracted in a ROI, for example a region of the default network (DN), and correlated with the rest of the brain to locate the entire set of DN regions using a model based approach (Biswal et al. 1995). The model consists of regressors of interest (seed time-series(s)) and numerous regressors of no interest (such as global signal, white matter, out of brain compartments, movement parameters) to increase signal to noise. Notably, the use of global signal regressors is debated, because they artificially produce anticorrelations (van Dijk et al. 2010). Other possibilities to control for noise include for example the monitoring of cardiac and respiratory response which can be included as additional regressors of no interest (Lund et al. 2006; Chang and Glover 2009a, 2009b) but were not applied in this thesis. The individual correlation maps were subsequently entered in a second level analysis for group inference like in standard univariate analysis (Friston et al. 1995). A seed based RSFC analysis was applied in Study 3.

3.4 Laterality indices

Laterality indices (LIs) were used as values to quantify relative difference in the engagement of the left versus right hemisphere regions and were applied in Study 3 to examine inter-hemispheric interactions during rest. They provide a mathematical quantification of lateralization. Traditionally, individual LIs are generated based on the following simple operation:

$$LI = \frac{\Sigma \text{activation}_{\text{left}} - \Sigma \text{activation}_{\text{right}}}{\Sigma \text{activation}_{\text{left}} + \Sigma \text{activation}_{\text{right}}}$$

[3]

To account for thresholding effects, the LI toolbox was used (version 1.2) (Wilke and Schmithorst 2006; Wilke and Lidzba 2007). It generates weighted mean LIs (LI_w s) iteratively exploring increasing thresholds using a multithresholded bootstrap-method. This method uses 20 thresholding intervals (from 0 to the max t-value) and generates 100 bootstrap samples with a resampling ration of $k = 0.25$ for each hemisphere. For all thresholds, a total of 10,000 lateralization indices were generated for surviving voxels for these samples. Only 50% around the central mean of these data were kept for robustness against outliers (single voxels with deviating high t-values). To get a more reliable LI, a higher weight was applied to higher thresholds according to the following equation [4].

$$LI_{\text{weighted}} = \frac{\sum_{i=1}^n W_i * LI_i}{\sum_{i=1}^n W_i}$$

[4]

where W_i is the t threshold at which LI_i was generated.

Individual weighted LIs thus favor regional activation, which shows higher correlation with the task (in our case functional connectivity with bilateral TP), such that they receive stronger impact on the resulting LI value.

4. Summary of empirical studies

In this section, all four studies constituting this thesis are summarized. The manuscripts can be found in full length in the Supplements (C).

4.1 Project 1

How music alters a kiss: superior temporal gyrus controls fusiform-amygdalar effective connectivity

While watching movies spectators integrate visual and auditory information to a coherent percept, thus paralleling important aspects of everyday emotional experiences. Both music (e.g. Koelsch 2013a) and film in particular (Gross and Levenson 1995) are known for their advantageous capacity to elicit strong emotions. In multisensory integration paradigms, it was shown that information in one modality can change the perception of the other (McGurk and McDonald 1976; de Gelder and Vroomen 2000; Ethofer et al. 2006), also called the emotional McGurk effect (de Gelder and Bertelson 2003). In movies, music is able to strongly impact the perception of complex dynamic visual stimuli (Vitouch 2001; Boltz 2005). To investigate the modulatory impact of emotional music during movie perception, we used kissing scenes from romantic comedies and happy-sad music pairs in combination with functional magnetic resonance imaging (fMRI) scanning and behavioral ratings.

Twenty-two right-handed healthy participants were presented with 24 kissing scenes, of which eight were combined with happy music, eight with sad music and eight without music (Fig. 2). For this purpose, a highly standardized auditory stimulus set was developed containing carefully selected happy and sad music pieces matched for pleasantness/unpleasantness, instrumentation, style and tempo. Because happy music is usually faster than sad music, leading to physiological effects such as increased heart rate and increased breathing rate (Bernardi et al. 2006), for each happy-sad pair, an electronic beat was composed and added to the original music. In a break of 42s between the film clips, the participants rated their own emotional state in terms of valence, arousal, happiness and sadness. Participants gave their ratings using a trackball to move a cursor on a white scale (valence scale -3 to +3; arousal-, happiness- and sadness scale 1-7) on a black background. For each item, they had to respond within 8s. With regard to stimulus

combination and order of presentation, we employed a fully randomized design, in which the 16 music pieces were allocated randomly to the film clips to avoid a constant combination of one film clip with a specific piece of music.

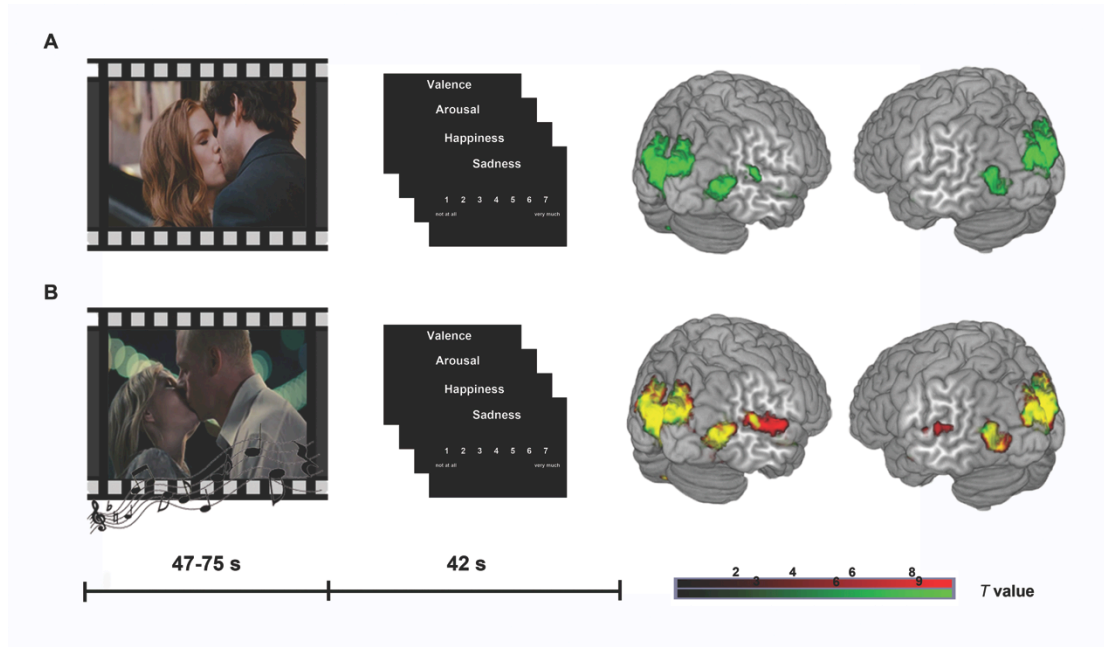


Figure 2 Experimental design and brain activations.

In the upper panel the mute kissing scenes are illustrated with behavioral ratings and respective brain activations (A, green). The lower panel depicts both audiovisual conditions (B, red). Additive overlay is indicated by yellow colored activations (B, yellow). All activations depicted $p < 0.05$ family-wise error (FWE) whole-brain corrected, cluster extent threshold $k > 5$ voxels.

The behavioral results showed that music had a modulatory impact on the emotional experience of the participants: paired t-tests for the ratings of happy and sad film-music pairs revealed significant differences between the evoked sadness and happiness (both p 's < 0.001) but no significant differences between valence and arousal. The fMRI analysis showed stronger blood level oxygen dependent (BOLD) signal changes in the anterior superior temporal gyrus (aSTG) for the happy music condition compared to the sad music one (Fig. 2, Fig. 3, Table 1).

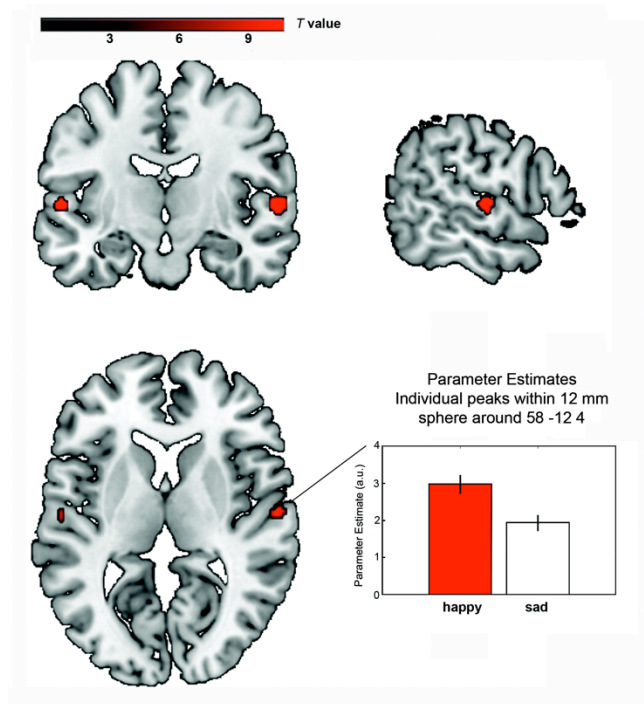


Figure 3 Emotion effect of happy vs. sad music.

The emotion effect of music (happy > sad) is located in the aSTG. The plot shows parameter estimates including betas at the individual peak within a 12 mm sphere around the group peak in the right aSTG with error bars indicating standard errors. All activations depicted $p < 0.05$ FWE whole-brain corrected, cluster extent threshold $k > 5$ voxels.

Table 1 Regional brain activation during the contrast happy vs. sad.

Region	Brodmann area	x	y	z	Cluster size	t value
happy music vs. sad music						
R. aSTG	BA 22	58	-12	4	32	10.43
L. aSTG	BA 22	-56	-14	4	22	10.11

Note: Reported regions show a significant activation at $p < 0.05$ whole-brain FWE corrected, cluster extent > 5 voxels.

This region has been identified as a region for multisensory integration (Damasio 1998; Calvert and Thesen 2004; Pourtois et al. 2005; Kreifelts et al. 2007), specifically for emotional material (Robins et al. 2009). To reveal an underlying mechanism of the observed univariate results, we applied nonlinear dynamic models of effective connectivity (DCM). A three-region network was investigated including the aSTG, the fusiform gyrus (FG) and the amygdala (AMY). The selection of the two

latter regions was motivated by the literature showing their engagement during multisensory integration of emotion (Baumgartner et al. 2006; Ethofer et al. 2006; Eldar et al. 2007) and by their activations in the present study during the presentation of movies with or without music. Dolan et al. (2001) reported increased hemodynamic responses in FG and AMY when fearful faces were presented together with a congruent vocal expression of emotion and assumed greater connectivity between AMY and FG during congruent audiovisual conditions than during incongruent conditions. Calvert and Thesen (2004) proposed the superior temporal gyrus as a heteromodal structure, which mediates modulatory influences on activity of other brain regions. We tested a gating effect of aSTG on fusiform-amygdalar connectivity in dependence of happy and sad music during movie perception. BMS revealed a winning model architecture with bilinear modulations of happy and sad music on neural propagation from FG and AMY to aSTG (Fig. 4). This was inhibitory and significantly increased for sad compared to happy music. The model also contained a suppressing gating of aSTG on FG to AMY connectivity, which was significantly increased during the happy music due to decreased inhibition of aSTG (Fig. 5).

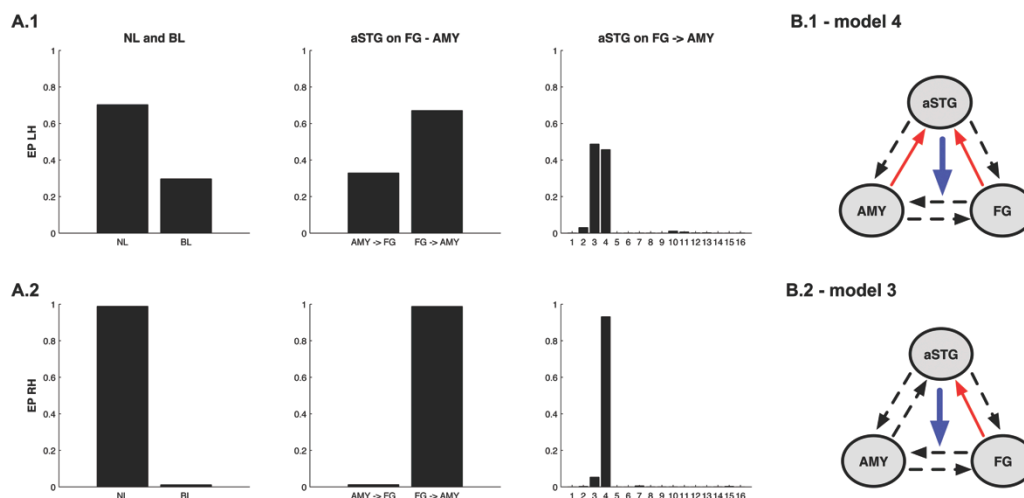


Figure 4 Bayesian model selection.

Results of BMS for the left hemisphere (LH, A.1) and the right hemisphere (RH, A.2). Exceedance probabilities (EP) are reported as a measure of relative model fit. From left to right: Family selection of bilinear (BL) and nonlinear (NL) model families, family selection of the two nonlinear families: aSTG on AMY to FG connectivity (AMY \Rightarrow FG) and aSTG on FG to AMY connectivity (FG \Rightarrow AMY) and model selection for the model-subspace containing 16 models with all possible combinations of happy and sad music modulation. The winning models are model 3 and 4 for the left hemisphere and model 3 for the right hemisphere with backward projections from AMY and FG to aSTG.

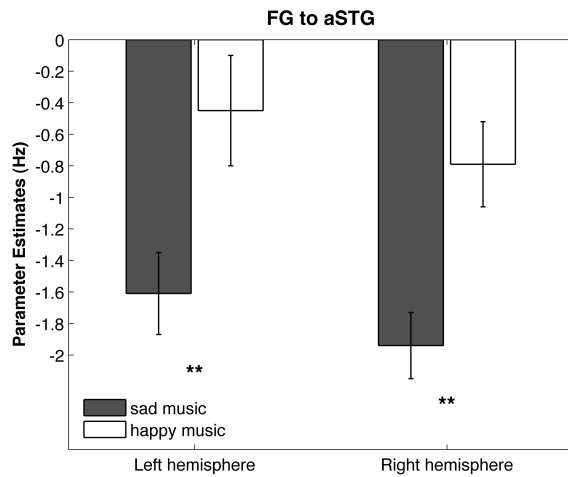


Figure 5 Bilinear modulation on the connection from FG to aSTG.

In both hemispheres, suppressing influence of sad music on the connection from FG to aSTG was significantly stronger for sad than for happy music resulting in enhanced neural propagation of the FG to AMY. Error bars indicate standard error. ** $p < 0.001$.

In conclusion, my co-authors and I have shown in Study 1 that music impacts the emotional experience of the spectators during movie perception. Neural correlates are found in a dynamic brain network that integrates multisensory emotional information, rather than in single functionally specialized brain areas. Fusiform-amygdalar coupling strength is modulated via feedback through aSTG, which was more pronounced for sad music showing that soundtrack valences may modulate emotion elicitation in movies by differentially changing preprocessed visual information to the AMY. Relating to AMY, this valence effect may function to decrease stimulus ambiguity. As a potential self-relevancy detector (Sander et al. 2003; Adolphs et al. 2010b) the AMY seems more involved through higher vigilance based on stimulus ambiguity (Whalen et al. 1998). According to Whalen et al. (1998), ambiguous or less explicit stimuli require the organism to gather more information to determine the appropriate behavior to engage in. Given that the kissing scenes are highly positive material, the combination with sad music may be perceived as more ambiguous and less congruent than with happy music.

4.2 Project 2

The temporal pole top-down modulates the visual ventral stream during social cognition

In extension of Study 1, Study 2 included an additional modulatory cue besides

music, the semantic context. In this study, we asked how the emotional reactions of the participants were modulated by emotion congruent music and by background information placing the presented film clips and the movie character in a narrative context. Therewith, we shifted the focus to mentalizing processes, more specifically on the empathic concern for the movie character, which constantly takes place during movie perception and is one of the core processes for emotion elicitation in movies (Raz et al. 2014). The temporal pole (TP) is specifically equivocal to be involved in these processes (see 1.4.2). Based on findings from semantic dementia (SD) showing that neurodegenerative loss in the anterior temporal lobe (aTL) is associated with progressive deficits in recognizing objects across modalities (Lambon Ralph et al. 2012; Binney et al. 2010; Visser et al. 2010a), the TP is considered as a domain general hub integrating semantic information from different modalities into a coherent representation (McClelland and Rogers 2003; Patterson et al. 2007). Furthermore, the TP has been associated with diverse functions of social cognition and emotion processing (Olson et al. 2007, 2013).

To test the semantic hub theory and the neuromodulatory role of TP in the context of social cognition, 26 participants were presented with a new set of stimuli consisting of 60 empathic film clips from feature films. The selection of visual stimuli was based on film theory. Plantinga (1999) describes a specific sort of scene, the scene of empathy, which is applied intentionally by film directors to elicit empathetic emotions in the viewer. This sort of scene utilizes a prolonged shot of the character's face to focus the attention on his or her interior emotional experience. Hence, the empathic film clips depicting a close-up of a character (30 males, 30 females) for 12s with a sad facial expression and no mouth movements during fMRI scanning (Fig. 6). The context stimuli consisted of short written texts and were used to place the character in a narrative situation before each film clip was presented. For every film clip, a sad and a neutral context were created. The sad context was based on the actual situation of the character in the movie and described difficult psychological circumstances (e.g. the recent loss of a loved person, getting informed about one's infertility). The neutral context was created describing the general set-up, in which the character is presented in the clip (e.g. sitting in a car, drinking a glass of water), to control for processing of non-emotional language. All contexts consisted of two sentences (20.0 ± 2.1 words, range 17-23) and were matched with regard to sentence structure, word number and reading time (see Fig. 6 for examples). Since the focus of this study was the semantic context, we used only one type of music, namely

emotion congruent sad music. Therewith we ensured high power by a sufficient number of trials with a reasonable length of scanning time. Systematic variations of music and context resulted in a 2×3 design (music: on off; context: sad, neutral, off) and six conditions (Fig. 6). The first condition showed a silent film clip only. The second condition started with a neutral context followed by a fixation cross (4-8s, mean 6.19s) and a silent film clip. The third condition started with a sad context followed by a fix cross and a silent film clip. Condition four, five and six were alike but included sad music played during the presentation of the film clip. To be able to determine neural activations due to multi- vs. unisensory processing, a purely auditory control condition was included, in which the sad music was presented during a 12s fixation cross. Furthermore, after every trial in each condition, a 5s fixation cross was presented followed by two ratings, in which the participants used a tracking ball to rate their current emotional state in terms of compassion (valence for music only) and being moved on a 7-point Likert scale (1 not at all, 7 very much) for 8s each (Fig. 6).

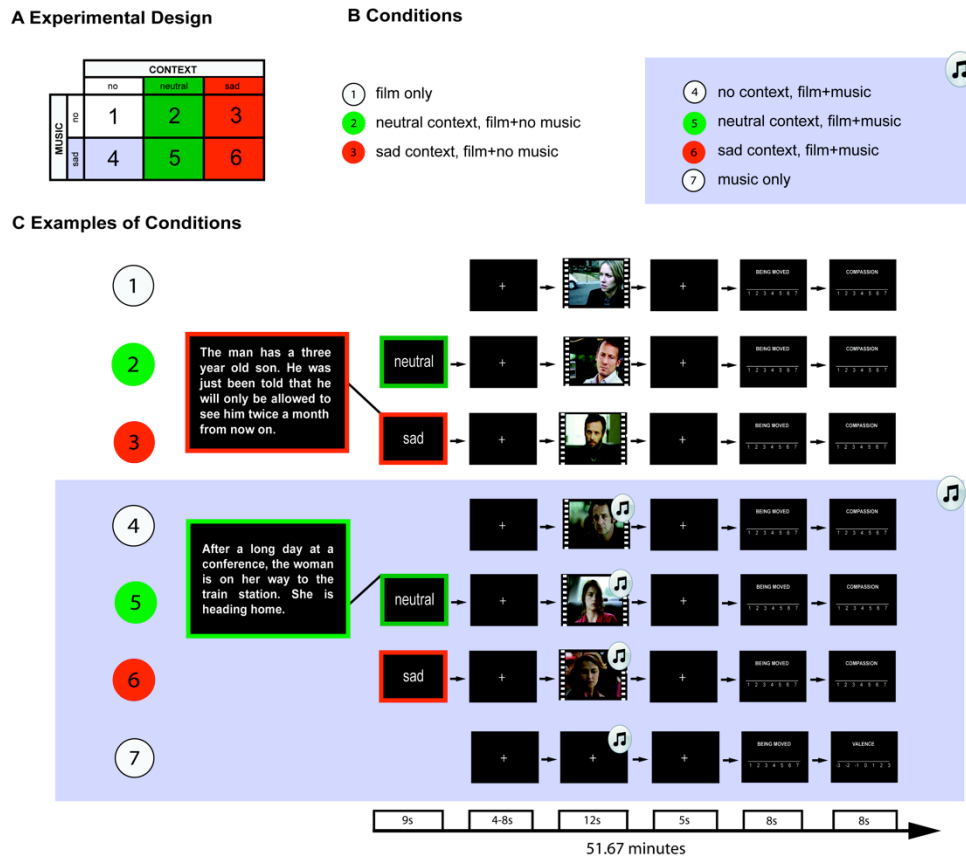


Figure 6 Factorial design and example of stimuli.

A, 2×3 Experimental design schematically depicting the two factors music (rows, no/sad) and context (columns, no/neutral/sad). B, Legend of conditions with no music (left) and with sad music (right). C, Examples illustrating the presentation order within each trial type. A fully randomized design was employed to present 70 trials in total (10 trials per condition).

It was assumed that sad context information increase the empathic concern of the participants with neural correlates in areas of the mentalizing network and brain areas for emotion processing and the processing of meaning. The results of behavioral ratings confirmed our hypothesis. 2×3 repeated-measures ANOVAs and paired t-tests showed that both music and context enhanced the compassion ratings of the participants (Fig. 7).

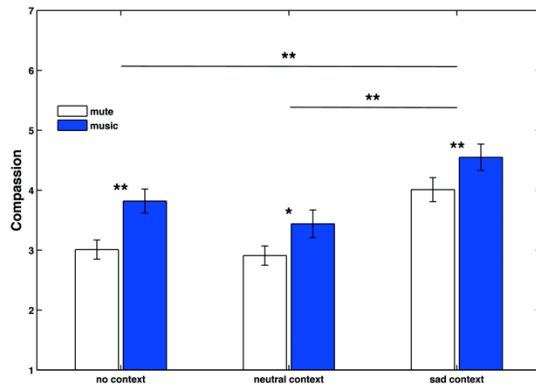


Figure 7 Behavioral results for an emotion effect of music.

Results of behavioral data. The emotional properties of the clips were rated in terms of compassion using a 7-point Likert scale (1 not at all, 7 very much). Music and sad context significantly increased the ratings. Error bars represent standard error of the mean. * $p < 0.05$, ** $p < 0.001$.

Furthermore, a mixed 2×3 factorial ANOVA revealed a main effect of context in primary visual areas, temporoparietal junction (TPJ), middle temporal gyrus and in TP (Fig. 8 A), consistent with the ventral visual pathway (Mishkin et al. 1983; Ungerleider and Haxby 1994) and the ventral stream of language processing (Hickock and Poeppel 2004), both implicated in the processing of meaning (Jeannerod and Jacob 2005; Carlson et al. 2014). Brain activations responsive to sad vs. neutral context conditions were found in TP bilaterally (Fig. 8 B) placing the TP at the core of social cognition, in line with the presumed role of TP in socio-emotional processing (Olson et al. 2013). The involvement of the TP in emotion processing of social stimuli is supported by the parametric analysis. This revealed a linear change of BOLD signal in the right TP and right superior and middle temporal gyrus as a function of experienced empathic concern (Fig. 8 C, Table 2).

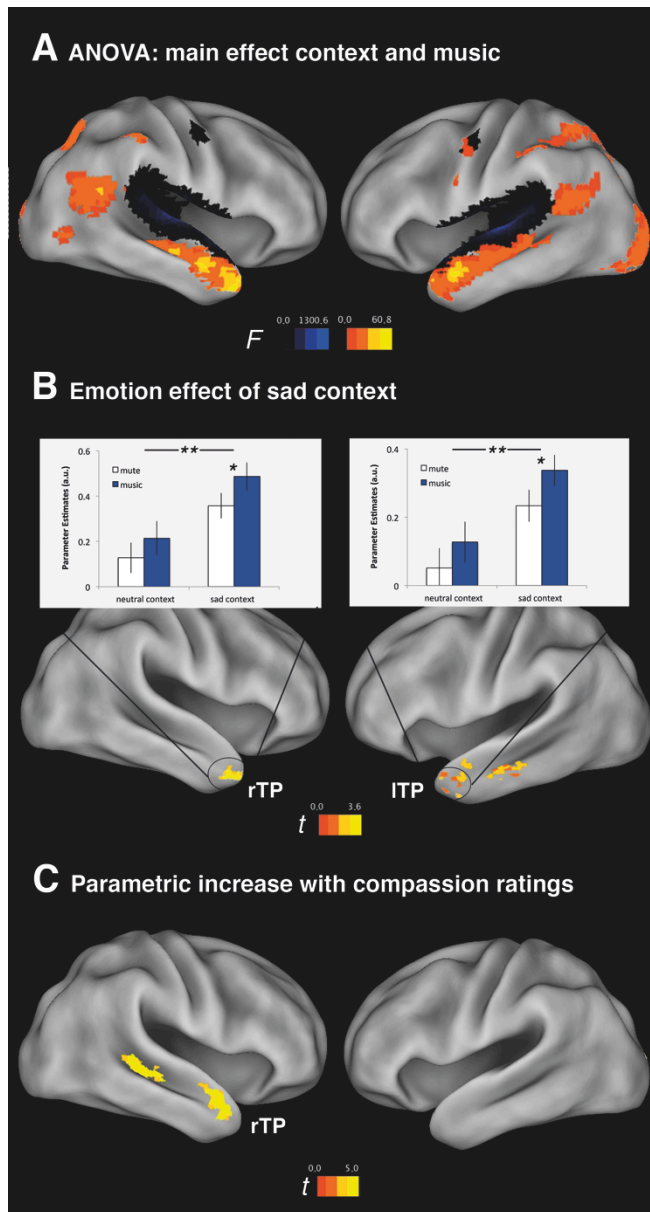


Figure 8 Regional brain activations during social cognition.

A, Music by context ANOVA: Main effect of context (red) and main effect of music (blue). B, Emotion effect of sadness during presentation of the film clips [sad context, film+music&sad context, film+no music] > [neutral context, film+music&neutral context, film+no music]; for display purposes depicted here at $p < 0.05$, cluster extent 10. C, Parametric modulation by compassion ratings in the MTG and aTL in the right hemisphere. Activations of A, and C depicted at $p < 0.001$, cluster extent 30, FWE corrected for multiple comparisons at cluster-level. The maps are projected onto a 3D brain surface using the Caret5 software.

Table 2 Cortical activations of sad vs. neutral context and parametric modulation with compassion ratings.

Region	Brodmann area	MNI coordinates			Cluster size	<i>T</i> value
		x	y	z		
		[sad context, film+music&sad context, film+no music] > [neutral context, film+music&neutral context, film+no music]^a				
R. temporal pole	BA38	39	12	-36	10	3.16
L. temporal pole	BA38	-42	9	-33	10	3.49
Parametric modulation with compassion ratings						
R. temporal pole	BA38	51	12	-27	62	5.04
R. temporal pole	BA38	54	6	-12		4.21
R. superior temporal gyrus	BA22	48	-33	3	54	4.86
R. superior temporal gyrus	BA22	48	-21	-3		4.41
R. middle temporal gyrus	BA22	57	-24	0		3.52

Significant clusters (defined at an uncorrected threshold of $p < 0.001$) that survive FWE correction ($p < 0.05$) at the cluster level are reported. Subpeaks $> 8\text{mm}$ from the main peak in each cluster are listed. ^a $p < 0.05$, small-volume FWE corrected.

Therefore, TP was included in the multisensory integration network which was investigated in Study 1 and tested again here using nonlinear dynamic causal modeling (DCM). We not only modeled a gating of aSTG on fusiform-amygdalar connectivity, but now also a gating of TP on FG to AMY connection. Bilinear effects were only modeled for connections including TP to elucidate how the information is processed between TP and FG as well as TP and AMY (Fig. 9).

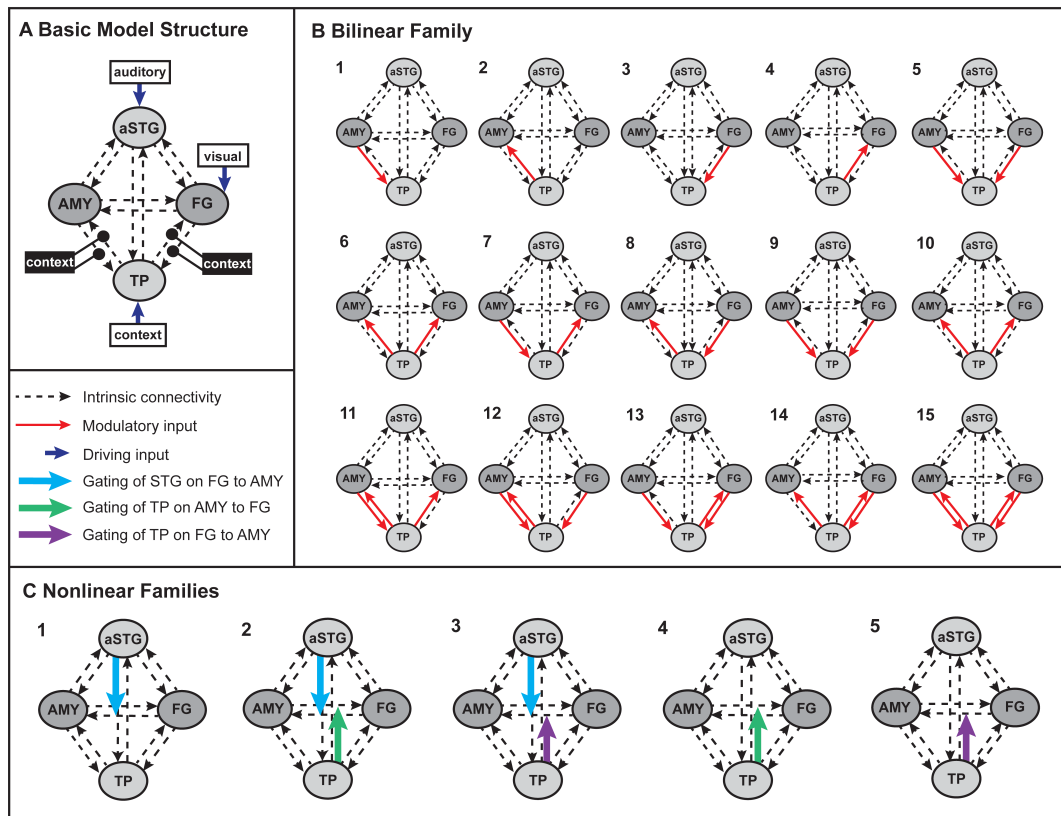


Figure 9 DCM modelspace - Study 2.

A, Basic model structure with nodes, intrinsic connections (dashed arrows) and driving input (dark blue arrows). The “visual” driving input on FG includes all conditions containing a film clip (Fig. 1 B 1-6). The “auditory” driving input includes all conditions containing music (Fig. 1 B 4-7). The “context” driving input includes all conditions containing context (Fig. 1 B 2-3, 5-6). For clarity the modulatory input is labeled “context”, which in fact contains the 4 distinct modulatory inputs (neutral/sad context followed by a silent film clip or a film clip accompanied by music). B, Bilinear model family with all possible bilinear modulations on TP-FG and TP-AMY coupling in both directions. C, Nonlinear families; the bilinear model family was tested in all of the nonlinear families resulting in 90 models per subject.

Based on findings from object recognition (Chan et al. 2011; Campo et al. 2013; Yvert et al. 2013), we expected backward projections from TP to antecedent regions of the ventral visual stream (i.e. FG). In line with our hypothesis, Bayesian model selection (BMS) revealed a gating of aSTG and TP on fusiform-amygdalar connectivity for the right hemisphere and a gating of TP on fusiform-amygdalar connectivity for the left hemisphere (Fig. 10). The winning model additionally contained bilinear modulations on the connectivity from TP to FG during the integration of contextual information for both hemispheres (Fig. 10). Inspection on parameter estimates revealed that these backward projections were enhanced by a simultaneous presentation of emotion-congruent music (Fig. 10).

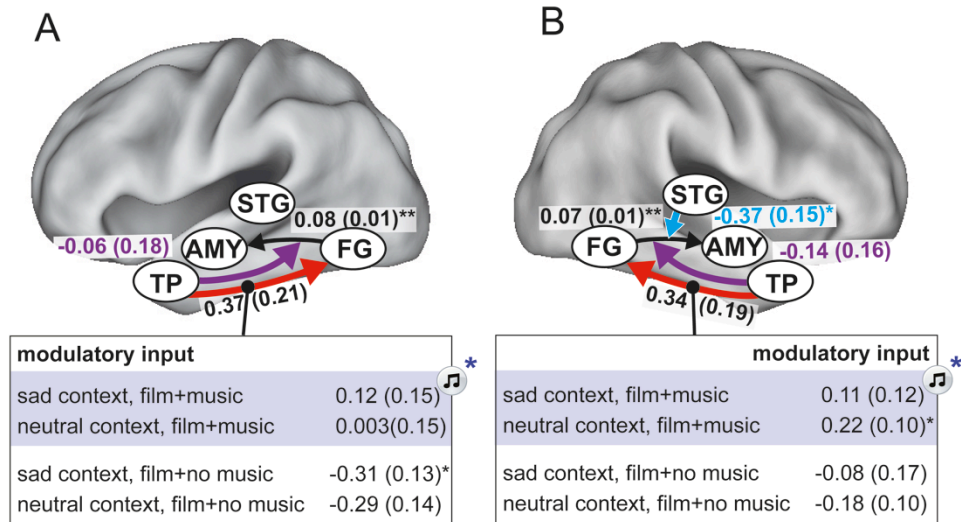


Figure 10 DCM connectivity parameters.

Mean parameter estimates indicating connectivity strength across participants (SEM) in Hz. A, Left hemisphere with a gating of TP (purple arrow) and right hemisphere (B) with a gating of TP and aSTG (purple arrow and light blue arrow) on FG to AMY connectivity. The parameter estimates of the endogenous connection from FG to AMY (black arrow) and TP to FG (red arrow) as well as the modulatory input of the four context conditions on TP to FG connectivity are listed (boxes below). Additive effects of modulatory parameters (boxes) on TP to FG intrinsic connectivity show that all context conditions increase effective connectivity from TP to FG in both hemispheres. ANOVA with parameter estimates of the modulatory input revealed a significant main effect of music (blue background) showing that top-down modulations of TP are increased by music. Regions converging multisensory stimuli are depicted in yellow. * $p < 0.05$, ** $p < 0.001$.

In sum, my co-authors and I have shown in Study 2 that visual, auditory and contextual cues impact the empathic concern of the study participants with neural correlates for brain regions involved in semantic and socio-emotional processing. Specifically, an emotion effect of sad context was found in TP together with top-down modulations to regions of lower-level processing in the ventral visual stream as a function of cue configuration (context and music). They underscore the importance for recurrent (bottom-up and top down) interactions for the integration of socio-emotional cues.

4.3 Project 3

Hippocampal-temporopolar connectivity contributes to episodic simulation during social cognition

In Study 2, the participants' empathic concern was tracked by activity in the right TP and bilateral anterior hippocampi (aHP) (Fig. 11 A2 (bottom)). This result was discussed by means of the episodic simulation hypothesis, namely that people use

own experiences to simulate other's thoughts and feelings to increase their empathic concern (Mitchell et al. 2006a; Ciaramelli 2013).

Multiple evidences point to episodic simulation as the cognitive process underlying the observed BOLD response in the right TP and bilateral aHP. Socio-emotional episodic simulation requires the integration of context-dependent AEM with context-independent semantic memory (SM). In the literature, the aHP was shown to be particularly involved in AEM (Maguire 2001; Gilboa et al. 2004; Moscovitch et al. 2006), whereas TP is involved in processing of SM (Rogers et al. 2006; Patterson et al. 2007; Binney et al. 2010). The results are also consistent with a functional segregation along the longitudinal axis of HP. The posterior part is associated with spatial memory (Pothuizen et al. 2004; Kühn and Gallinat 2013) and the anterior part with emotion processing (Fanselow and Dong 2010; Koelsch 2013a), which is an essential component of AEM (Dolan et al. 2000).

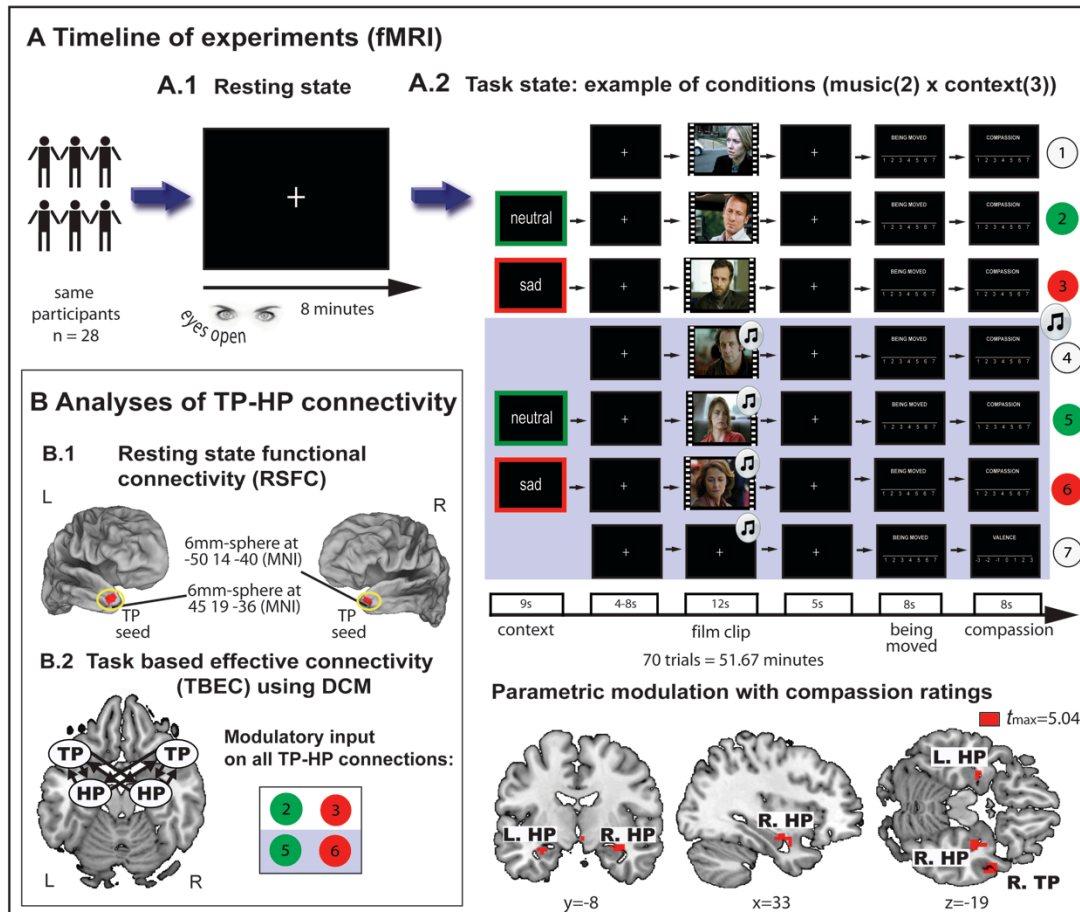


Figure 11 Timeline of experiments, previous fMRI results and present analyses.

A, The same participants underwent the measurement of fMRI data during 8min of resting state (fixation cross, eyes open) (A.1) followed by 51.67min of a social cognition task (A.2), in which the presentation of empathic film clip was varied by the factors music (off/on (blue background)) and context information preceding the film clips (neutral(green)/sad(red)) resulting in 6 conditions and a control condition with music only (A.2, 7). After the film clips the participants rated their emotional experience in terms of *being moved* and *compassion* on a 7-point Likert-scale (1 *not at all*, 7 *very much*). A parametric modulation with compassion ratings revealed activations in bilateral anterior HP and right TP (A.2 bottom) suggesting episodic simulation as cognitive process underlying an increase of empathic concern for the movie characters. B, To investigate the contribution of TP-aHP connectivity to episodic simulation, a functional connectivity analysis was applied to resting state data (B.1) by looking for correlations of the fMRI time-series of bilateral TP with each voxel in the rest of the brain. TP-HP effective connectivity was examined during task using DCM. This analysis tested the hypothesis that TP-aHP connectivity changes as a function of context information and episodic simulation.

Study 3 set out to map episodic simulation onto the connectivity of two brain regions, which are key for processing of different memory types: the TP, implicated in SM, and the hippocampus (HP), implicated in AEM. This was done during internally (rest) and externally (task) driven cognition using two different methods to investigate TP-HP (functional and effective) connectivity, namely resting state functional connectivity (RSFC) and task-based effective connectivity (TBEC) (Fig. 11 B.1, B.2) using the same task as in Study 2, while context information was thought to trigger

episodic simulation (Mar et al. 2011b). RSFC was included in Study 3, because unconstrained cognition during rest is associated with episodic simulation involved in cognitive operations like thinking about the past, planning the future, making decisions or making inferences about mental states of others (Buckner 2010; Spreng and Grady 2010a; Schacter et al. 2012). The most prominent network associated with these processes is the default network (DN) (Andrews-Hanna 2010), of which TP and aHP are crucial parts (Greicius et al. 2004; Andrews-Hanna 2010) (2.4).

The RSFC analysis (i.e., intrinsic correlations in activity between brain areas in the absence of overt stimulation or task demands) (Biswal et al. 1995) was performed with seed regions in bilateral TP (Fig. 11 A.1, B.1). TBEC was examined using DCM on an 8-region network including both left and right hemispheric aHPs and TPs. A set of 15 models was fitted to the data, each assuming different modulatory input on TP-HP connections within and across hemispheres to examine changes in effective connectivity between TP and aHP as a function of context and episodic simulation (Fig. 11 B.2, Fig. 12 B). The models were stratified in three model families with forward connections (TP to aHP), backward connections (aHP to TP) or recurrent connections (in both directions) to determine the direction of AEM with SM integration (Fig. 12 B, C, D) (for details on methods see original research article in the Supplements C).

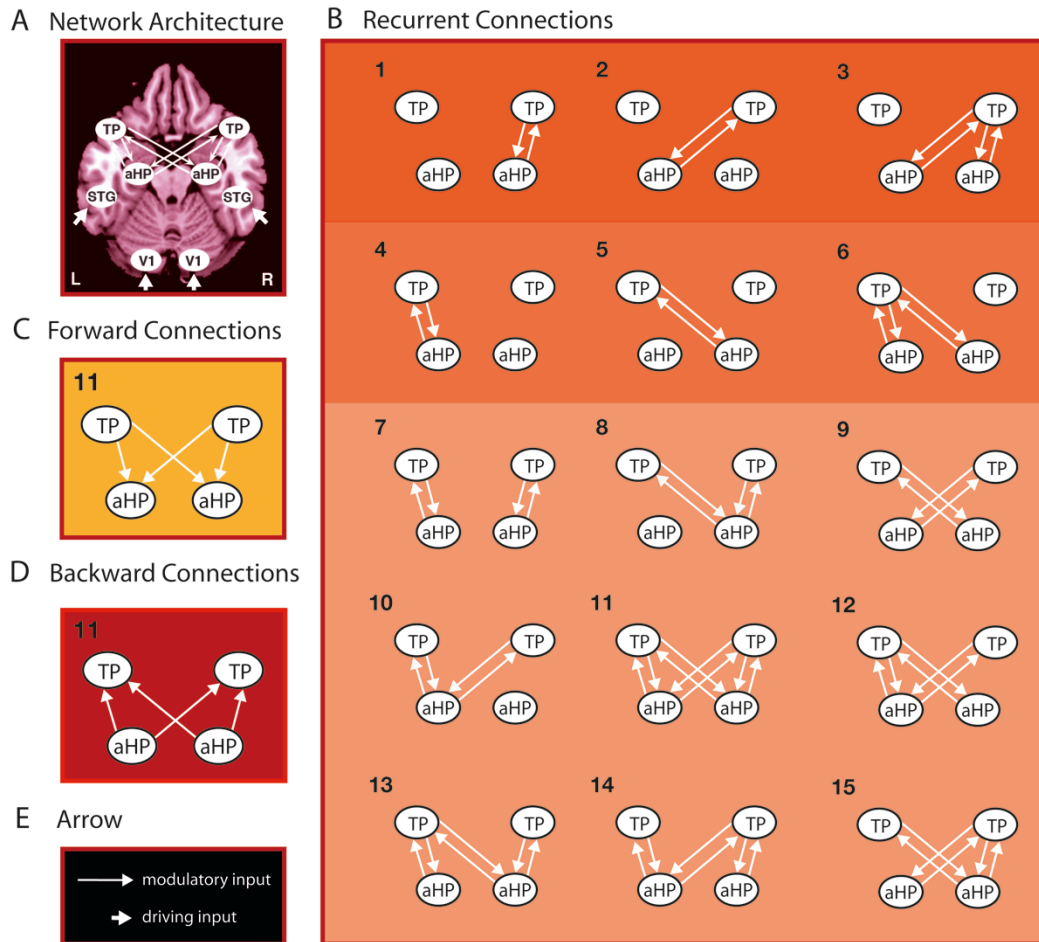


Figure 12 DCM modelspace – Study 3.

A, Basic model structure depicting all nodes of the bilateral symmetric network with driving input on V1 and STG (short arrows) and bilinear modulations between aHP and TP (long arrows). B, Model-subspace showing all possible variations of bilinear modulations with recurrent connections. These 15 models were additionally modeled in a subspace with forward connections (C, from TP to aHP) and a subspace with backward connections (D, from aHP to TP) only.

As described above, we hypothesized a particular crossed-hemispheric connectivity between right TP and left aHP, assuming that episodic simulation is mediated by the lateral specialization of the key structures involved. Furthermore, we expected to find evidence of an inter-hemispheric coupling of left aHP and right TP in two different functional states. This was based on the evidence that episodic simulation occurs during both resting state and complex social cognition as in our empathy task. Therewith we followed Cole et al. (2014), who found that the same intrinsic brain architecture shapes extrinsic neural connectivity.

Consistent with its presence in the DN, left and right TP showed RSFC to main DN regions, namely the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), as well as the TPJ, and to the extended DN, namely the middle

temporal gyrus (MTG) and the TP bilaterally ($p < 0.05$, whole-brain FWE corrected, cluster extent > 10 voxels; Fig 13 A.1). In distinction to the left TP, the right TP showed additional functional connectivity to aHP bilaterally and to the right AMY (Fig 13 A.2).

A region of interest (ROI) analysis for HP was conducted using a map of t -statistics containing the connectivity pattern from TP bilaterally. Averaged individual parameter estimates within a 10mm sphere around individual peaks within anatomical masks of the HP show significantly stronger connectivity of left and right HP to the right TP than to the left TP (p 's < 0.05) (Fig. 14 A). This is a remarkable result considering the fact that ipsilateral connectivity is generally stronger than contralateral connectivity and emphasizes the strong crossed-hemispheric coupling of right TP and left HP.

The results were substantiated by identical analyses in another independent data set of 198 participants, taken from the freely accessible database "1000 Functional Connectomes Project" (http://www.nitrc.org/projects/fcon_1000/) (Biswal et al. 2010). RSFC to bilateral aHP was more pronounced for the right TP (Fig 13 B.2). Averaged individual parameter estimates show significantly higher connectivity of left and right HP to the right TP than to the left TP (p 's < 0.001) (Fig 14 B).

To quantify laterality differences of whole brain TP-RSFC, weighted laterality indices (LI_w s) were calculated for the Berlin sample within symmetric bilateral masks for our key regions (TP and aHP) and for the DN consisting of PCC, mPFC, TPJ, MTG, aHP and TP. LI s quantify relative differences in left versus right hemisphere activations. LI_w -values lie on a continuum between +1 (only left) and -1 (only right). The results revealed a right lateralization in the DN ($-0.36 \pm 0.02(\text{se})$) and TP (LI_w -mean $-0.38 \pm 0.02(\text{se})$), but a left lateralization in aHP ($0.25 \pm 0.08(\text{se})$) (Fig. 15).

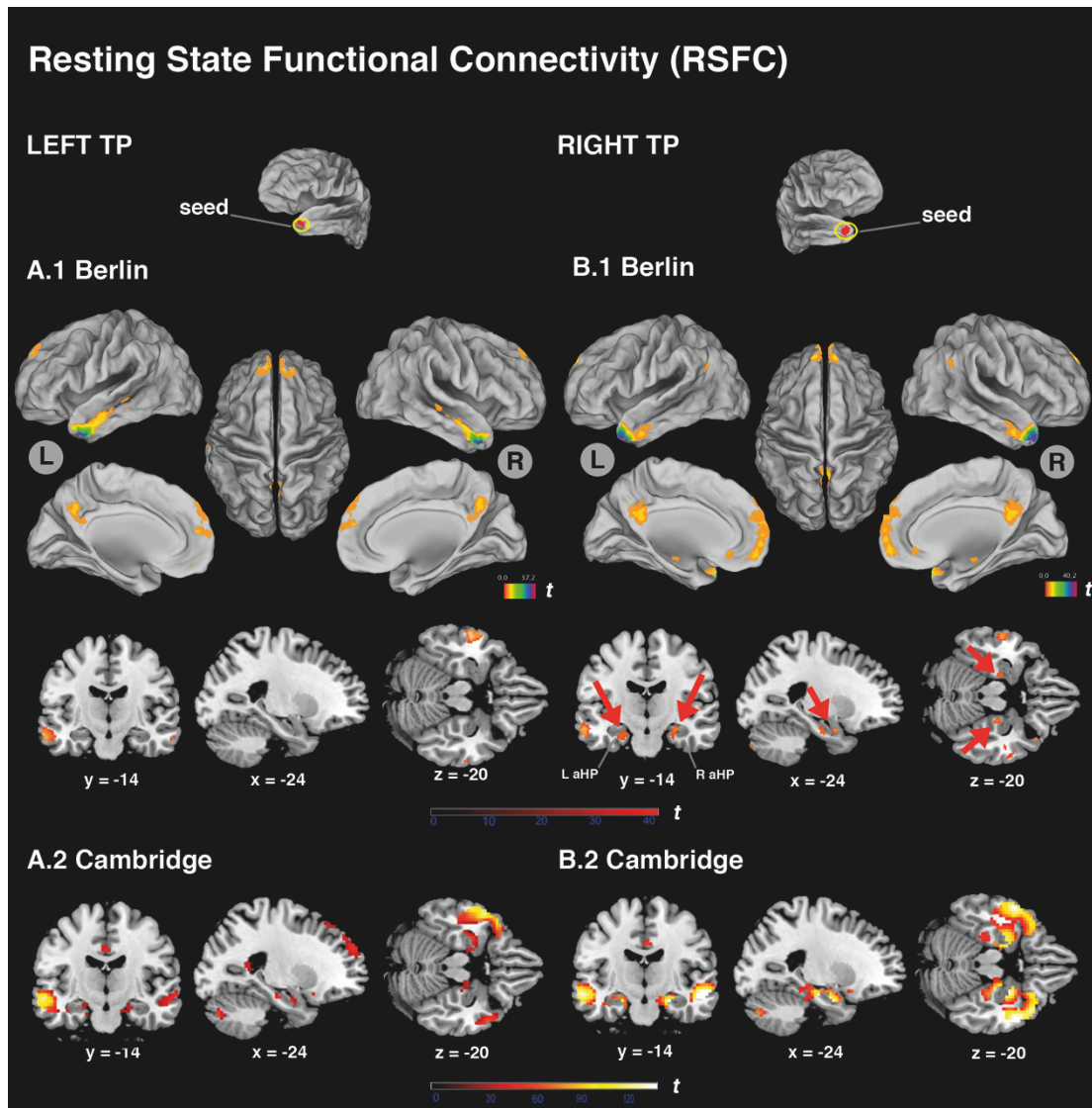


Figure 13 Resting state functional connectivity.

A.1, Connectivity pattern of left TP seed (see yellow ellipse in top left panel) superimposed on left (L) lateral and medial, dorsal, and right (R) lateral and medial views and on coronal, sagittal and transaxial brain sections (below). B.1, Connectivity pattern of the right-hemisphere TP seed; red arrows indicate RSFC to aHP bilaterally. A.2, RSFC of the same analysis in an independent data sample (Cambridge sample, $n = 198$) showing the connectivity pattern of left TP, superimposed on the same coronal, sagittal and transaxial brain sections. B.2, RSFC of the right TP seed in the Cambridge sample. Coordinates on the bottom refer to MNI space. T-maps of resting-state connectivity are thresholded at $P < 0.05$ FWE whole-brain corrected, cluster extent threshold $k > 10$ voxels.

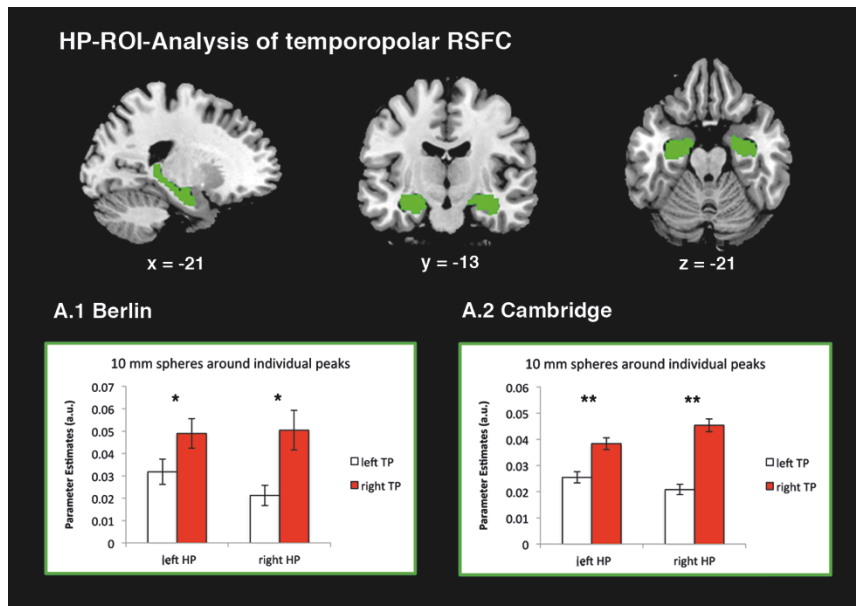


Figure 14 ROI analysis of HP.

Sagittal (left), coronal (middle) transaxial (right) sections depicting HP-ROI (green) taken from the anatomic labeling atlas. Coordinates refer to MNI space. Bar plots depict averaged parameter estimates within a 10 mm sphere around individual peaks within left and right HP-ROIs of the Berlin data sample ($n = 28$) (B.1) and Cambridge sample ($n = 198$) (A.2). Error bars represent standard error of mean.

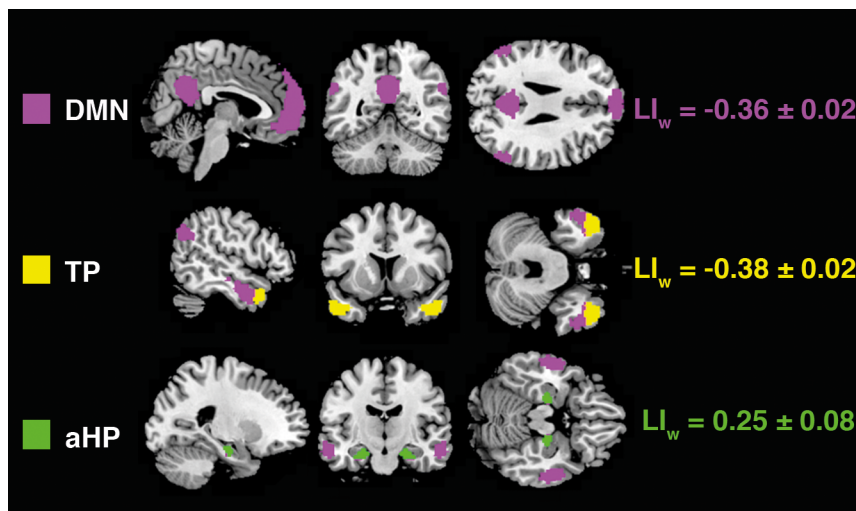


Figure 15 LI analysis.

ROIs covering the DN (top, violet), TP (middle, yellow) and aHP (bottom, green) with weighted LI group means on the right and standard errors of the mean. For LI_w -calculations were applied to RSFC patterns of bilateral TP. LIs vary between -1 (right lateralization) and +1 (left lateralization). To note, green and yellow colored ROIs were also part of the DN mask (violet).

The results of TBEC confirm and extend the RSFC-results since conclusions on directionality are only possible by TBEC. Random-effects family-based inference comparing backward, forward and recurrent families (Fig. 16) revealed that the backward family (from aHP to TP) clearly outperformed the forward and the recurrent family with an EP of 66.44% (Fig. 16). The subsequent model comparison within the

backward family revealed the most plausible model with backward projections from left aHP to right TP with an EP of 68.56%, compared with exceedance properties of $\leq 8.6\%$ for all of the 14 models of the comparison (Fig. 16). The winning model structure indicates that activity in left aHP causes changes of activity in right TP as a function of context information.

Consistent with our hypothesis and with the results of RSFC analysis, the TBEC analysis strikingly corroborates a coupling of left aHP and right TP during episodic simulation.

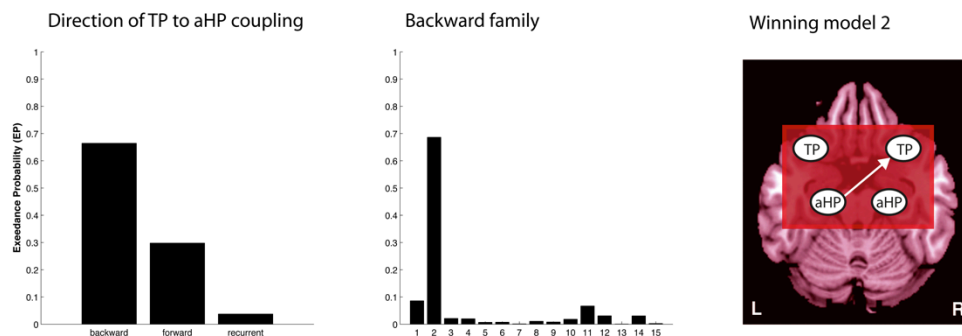


Figure 16 Results of Bayesian model selection.

BMS was performed on two levels. Family selection of backward, forward and recurrent modulation of TP to aHP connectivity (left) and model selection for the backward model-subspace containing 15 models, with all possible combinations of context modulation on aHP to TP connections (middle). Exceedance probabilities (EP) are reported as a measure of relative model fit.

In sum, the results demonstrated by my co-authors and me in Study 3 point to a novel inter-hemispheric mechanism for episodic simulation. Hemisphere specific allocation to memory sub-functions demonstrates how lateral specialized brain regions are systematically coupled during higher-order cognitive demands. The retrieval of self-referential episodic memory was proven as highly beneficial empathy processes, suggesting a putative impairment of the neural mechanism in psychiatric diseases with deficits in socio-emotional processing such as autism spectrum disorder (ASD) and should be tested in prospective studies.

4.4 Project 4

The quartet theory: Implications for autism spectrum disorders.

Comment on “The quartet theory of human emotions: An integrative and neurofunctional model” by Koelsch et al.

In Project 4 we commented on the Quartet Theory of Human Emotions (QT; Koelsch et al. 2015) and addressed a psychiatric disorder that is characterized by problems in social and emotional functioning, namely ASD. As described above (2.5) the QT states that emotion percepts are generated in the brain by interaction of 4 affect systems: The brainstem-centered system, the diencephalon-centered system, the hippocampus-centered system and the orbitofrontal-centered system. The hippocampal system is thought to be responsible for attachment related affects, which indicates a likely disruption of this system in ASD, characterized by social and communication deficits, decreased sensitivity to social and emotional cues as well as restricted and repetitive behaviors. Detachment related behavior like social withdrawal, avoidance or indifference to affection or physical contact is also common. By contrast, the orbitofrontal-centered affect system is thought to perform “a fast and automatic (non-conscious) cognitive appraisal of both external and internal information” and is “involved in the control of emotional behaviour” (Koelsch et al. 2015). The role of the orbitofrontal-centered system is to evaluate sensory cues “with reference to internalized knowledge” (Koelsch et al. 2015). It thus interacts with the hippocampal system by integrating current sensory information with memory content provided by the hippocampal system. In healthy individuals, a successful integration of hippocampal memory is essential for top-down regulatory influences by the orbitofrontal cortex (OFC) on lower level sensory and other processing streams, such as the AMY, which is a target area for self-regulation in socio-emotional contexts (Bachevalier and Loveland 2006).

Taking the QT as a model to explain socio-emotional difficulties in ASD, the comment hypothesizes a dysfunctional interaction between the hippocampal- and the orbitofrontal-centered affect systems.

Pathophysiological evidence corroborates dysfunctional interactions of these two affect systems. Studies using rodent models of ASD have shown that impaired social behavior is associated with alterations of glutamate receptor concentrations in hippocampal and frontal cortices induced by disruptions of candidate ASD genes (e.g. Finlay et al. 2015). Interestingly, morphometric studies in ASD draw an inconclusive picture on hippocampal volume in this disorder (Stigler et al. 2011). However, the frontal cortex, including the orbitofrontal region, has been shown to be a main target area of early brain overgrowth in ASD (Carper and Courchesne 2005). In addition, malformations in the frontal cortex through neuroinflammatory responses or migration defects seem to persist regardless of developmental influences

(Courchesne and Pierce 2005). A dysfunctional interaction of the hippocampal and orbitofrontal system is also in line with the underconnectivity hypothesis in ASD which posits impaired large-scale connections of the frontal lobe, and implicates reduced integration of information and reduced control over lower-level systems (Courchesne and Pierce 2005). Structurally, the OFC and hippocampal systems are connected via the uncinate fasciculus, a pathway involved in memory and higher-order socio-emotional processing, which connects the OFC with the aTL and the rhinal cortex, which in turn is connected to the HP (von der Heide et al. 2013). Studies using diffusion tensor imaging to characterize microstructure in white matter tracts have repeatedly reported disruptions of the uncinate fasciculus in ASD (e.g. Ameis et al. 2011) supporting the long-distance underconnectivity hypothesis (Happé and Frith 2006) and in particular the potential dysfunctional interaction of the hippocampal and orbitofrontal systems. It was concluded that a dysfunctional interactions would result in insufficient integration of memory content provided by the hippocampal system resulting in reduced top-down control during cue-integration exerted by the OFC. This was further linked to deficits in emotion regulation in ASD. A dysfunctional interaction of the two affect systems might indirectly influence downstream regulation of the OFC to the AMY, which is a key process underlying emotion regulation in ASD (Pitskel et al. 2014).

Finally, we proposed some questions that would be interesting for future research from the perspective of the QT. It might be interesting for example to test how other affect systems (e.g. brainstem, diencephalon) or coordinate systems (e.g. the AMY) exert protective influence on the hippocampal system during stressful situations in ASD. The extent to which accessibility and vividness of memory retrieval and integration helps individuals with ASD to regulate their emotions using cognitive reappraisal might also bear examination in future research.

Taken together, my co-authors from Project 4 and I have used the QT to generate hypotheses on dysfunctional integration in ASD and refer to pathophysiological evidences from the literature to suggest that ASD might indeed be a neurocognitive integration disorder.

5. General discussion

The central question of this thesis is on the process in which different pieces of dynamic sensory information, i.e. visual, auditory and contextual cues modulate socio-emotional processing and underlying neural network dynamics. For this purpose, naturalistic social stimuli (film clips) were presented in different cue configurations (with or without music and with or without emotional/neutral context information) while brain activity was measured with functional magnetic resonance imaging (fMRI). Subjective emotional experiences were measured with self-report ratings inside the scanner after stimuli presentation.

Having summarized the four projects in the previous section, the results will now be discussed in relation to the five principal research questions (2.). Thereafter, a tentative neurobiological model is suggested describing the integration processes in the human brain, the neurobiological model of socio-emotional cue-integration (5.2). The model will be related to previous research, will be used as framework to discuss the thesis' discoveries in more depth and will be used to pave the road for future directions.

Finally, the model is used to generate upcoming research questions, listed in Table 3, together with more general questions that might be of future importance for the field of social and affective neuroscience.

5.1 Discussion of research questions

Integration of visual and auditory cues

The first question centers on the modulatory impact of emotional music. Study 1 and Study 2 were of relevance for this question. In Study 1, kissing scenes were presented with different types of music (happy, sad, or without music). In Study 2, empathic film clips were either presented with sad music or without music. Both studies provided strong evidence for the power of music in emotion elicitation, specifically its modulatory impact on the participants' experienced emotions. It was shown that music is integrated in so-called convergence regions and in turn has a neuromodulatory influence on the connectivity between other brain regions involved in visual and emotion processing. Music increases the empathic concern of the participants towards the movie characters (see blue bars in Fig. 7). Music also enhances top-down modulations from the temporal pole (TP) to lower processing

levels within the ventral visual stream (i.e. FG) (for response of TP to music see bar graph in Fig. 9 B). This shows that music increases the integration demand in the brain by transferring meaning to visual information and crucially impacts emotion processing. The importance of music for mentalizing is consistent with the results of previous studies (Eldar et al. 2007; Steinbeis and Koelsch 2009).

Integration of visual, auditory and contextual cues

The second question centers on the modulatory impact of context information on audiovisual integration and emotion. This question was investigated in Study 2. Study 3 also examined the modulatory impact of context, but specifically with regard to memory processes, which is addressed by the third question. To examine the second question, movie characters were embedded in a contextual frame. It was shown that sad emotion-congruent context information increased the empathic concern of the participants. This effect was tracked by activity in the ventral visual stream, the so-called 'meaning pathway' (Hickock and Poeppel 2004) and specifically in the TP. It was shown that the TP integrates multisensory information and top-down modulates the ventral visual pathway as a function of context information. We therefore found empirical evidence in support of Damasio's theory of retroactivation (i.e. convergence regions), the semantic hub account as well as for top-down facilitation models in complex social cognition (see 5.2).

Episodic simulation

Context information was assumed to trigger episodic simulation, the use of own experiences to infer about others' mental states. The underlying operation is an integration of different memory types, namely semantic memory (SM) with autobiographic episodic memory (AEM). The third question revolved around episodic simulation assuming that mnemonic integration might be instantiated in changes of connectivity between brain regions that are key for different memory types, i.e. the right TP for SM and the left anterior hippocampus (aHP) for AEM. Study 3 showed a distinct inter-hemispheric mechanism for episodic simulation. Backward projections from the left aHP to the right TP were increased in the presence of context information when participants were presented with the empathic film clips. This result was consistent to a coupling of the right TP with left aHP during resting state as revealed by functional connectivity analyses. Study 3 pointed to the relevance of inter-hemispheric interactions for advanced memory-based social cognition. The

retrieval of self-referential episodic memory was shown to play an important role for empathic responses stressing the importance of memory processes for social cognition (5.4).

Internally vs. externally driven cognition

The fourth question centers on differences of brain organization during different functional states in which the subjects were being scanned (rest and task). In everyday life, internal (being focused on the internal world) and external processing (being focused on external cues) modes naturally fluctuate over time (Smallwood et al. 2008). Consistently, intrinsic brain architecture is conceived as a neural baseline activity, a standard state of the brain, which shapes and prepares extrinsic (task-induced) network architectures and replays extrinsic activity during rest (Fox et al. 2006a; Vincent et al. 2007; Smith et al. 2009; Raichle 2010; Deco and Corbetta 2011; Hartzell et al. 2015). Even though Rehme has shown differences between functional and effective connectivity (Rehme et al. 2013) during a motor task, Study 3 provided strong evidence for state-dependent similarities between intrinsic and extrinsic connectivity. A main reason might be the social nature of our task, which is known to recruit default network (DN) regions (Mars et al. 2012), the network involved in internal mentation (Andrews-Hanna 2012). Our results are also in line with a study by Cole et al. (2014), who have compared functional connectivity at rest and during multiple tasks (social, emotional, n-back, motor etc.) and revealed a striking overlap of intrinsic and extrinsic network activity irrespective of task and in different independent datasets.

Impaired cue-integration in autism spectrum disorder

The fifth question centers on a potential dysfunctional cue-integration and its implications for psychiatric disorders. Based on the quartet theory (QT), we postulated a dysfunctional interaction of the hippocampal and the orbitofrontal affect systems in autism spectrum disorder (ASD). A review of pathophysiological findings in both systems has indeed shown that ASD might be characterized by a dysfunctional interaction of both systems. A focus on impaired cue-integration has implications for other disorders featuring social deficits like for example alexithymia and schizophrenia.

5.2 A neurobiological model of socio-emotional cue-integration

In the previous section, the results of the four projects were used to answer the five main research questions. Evidence was presented that can be linked to neurocognitive integration mechanisms as outlined in the Introduction section. This will be developed here when introducing a neurobiological model for socio-emotional cue-integration (Fig. 17). The model integrates the findings of our studies in order to connect and specify the integration mechanisms that were listed unsystematically in Figure 1.

Based on the research questions and findings of the thesis, a tentative theoretical model is proposed, the neurobiological model of socio-emotional cue-integration (Fig. 17). It combines mechanisms for neurocognitive integration with socio-emotional cognition and integrates the present findings into an interplay of mechanisms, which can be used to generate future research questions to be tested (Table 3).

Compared to Figure 1, the neural mechanisms are now connected and systematically arranged to illustrate potential interactions of mechanisms. The links that were empirically supported by our findings are highlighted in white. The socio-emotional cues manipulated in the studies are highlighted in red, which are the visual system (presentation of the movie clips) and the auditory system (presentation of music). In addition, memory processes were triggered by top-down contextual information that were presented prior to the film clips via the visual system (short written texts).

An underlying assumption of the model is that neural integration takes place in dynamic brain networks and not in functionally specialized brain regions. Single brain regions may have different roles in processing specific aspects within networks (i.e. functionally specialized regions), but they do not work in isolation, which can be observed in changes of connectivity between regions. This is in line with the theory of multiregional retroactivation (Damasio 1989), which states that different convergence regions bind information from different modalities at different levels of complexity with permanent interactions and reciprocities as well as neuromodulatory influence (i.e. modulations of activity of other neuronal populations) on other processing streams (Damasio et al. 1989, 2004). Music accompanying the kissing scenes was integrated in the anterior superior temporal gyrus (aSTG), a multisensory convergence region for emotion operating on a lower level within modality specific cortices. In addition, a

gating effect of aSTG on the connectivity between other brain regions involved in visual and emotion processing (fusiform gyrus (FG) to amygdala (AMY)) corroborated the neuromodulatory function of convergence regions. Consistently, Müller et al. (2012) found that a region in the posterior superior temporal sulcus integrated multisensory information and gated neural input from FG to AMY using static pictures of facial expressions and simple sounds (happy, fearful, sad, neutral). However, previous studies lacked the evidence of such a gating structure for naturalistic viewing conditions. Music was not only integrated in lower-level convergence regions but also in higher-order convergence regions, namely the TP. According to semantic hub accounts, the aTL including TP integrates information from multiple modalities and assigns conceptual meaning to perceptual input (McClelland and Rogers 2003, Patterson et al. 2007). Semantic hub accounts refer to the TP as convergence region, the difference, however, is that Damasio (1989)'s approach assumes multiple convergence regions implicated in semantic memory (SM). In addition, semantic hub accounts propose that the aTL integrates information but they do not discuss what happens after perceptual information is successfully encoded. However, a meaningful percept, which is imbued with SM, has to be made accessible for other processing streams, involved for example in emotion processing and behavior or lower-level perceptual processing. This thesis shows, for the first time in complex social cognition, that convergence regions top-down modulate modality-specific processing streams as a function of context information and integration demands. Study 2 showed that the TP top-down modulates information processing in lower-level processing areas within the ventral visual stream (i.e. FG) as a function of contextual framing and task demands, a process conceptualized by top-down facilitation models (Ullman 1995; Bar et al. 2003, 2006). Top-down facilitation models were developed in the context of object recognition and account for recurrent feedback connections in the ventral visual pathway (Ullman 1995; Bar et al. 2003, 2006; Simmons and Barsalou 2003). In Study 2, musical information increased task demands by providing additional perceptual information from another modality. Music has a strong capacity to elicit emotions (Koelsch 2013a; Blood and Zatorre 2001), to modulate emotion processing of dynamic visual stimuli (Eldar et al. 2007; Pehrs et al. 2014) and to trigger mentalizing processes (Steinbeis and Koelsch 2009; Parsons et al. 2014). The importance of musical meaning is also supported by studies on semantic dementia (SD). Patients with SD show deficits in recognizing musical emotions and are impaired in attributing affective mental associations to musical

stimuli to the degree to which they show atrophy in the aTL (Omar et al. 2011; Hsieh et al. 2012; Downey et al. 2013).

Facilitation models are neuroanatomically supported by demonstrations of recurrent pathways in macaque monkeys (Gilbert and Li 2013; Kravitz et al. 2013) and functionally supported by studies showing increased feedback-projections from prefrontal and anterior temporal regions to posterior temporal areas with increasing semantic integration demands during object recognition (Tyler et al. 2004; Chan et al. 2011; Clarke et al. 2011; Yvert et al. 2012). In these studies, integration demands refer to rising complexity like word recognition compared to phoneme detection and object recognition on different levels of specificity (basic vs. domain). A lesion study by Campo et al. (2013) corroborates the importance of top-down modulations from TP by showing that backward projections during naming of pictures are reduced in patients with atrophy in aTL.

In sum, we extend semantic hub accounts with top-down facilitation models that were transferred from object recognition to higher-order social cognition. We thus accounted for hierarchical reciprocal processing for cue-integration (Fellemann and Van Essen 1991; Kravitz et al. 2013) in line with Damasio's framework (1989). Top-down facilitation in a social context during semantic and emotion processing highlights the involvement of TP and elucidates its function as a semantic hub (see 5.4).

Moreover, we showed that the more socio-emotional cues converge, the stronger the emotional reactivity of the participants. This is in line with current models of cue-integration that conceive social cognition as an integrative process over multimodal cues and processing streams in order to develop Bayesian models of social cognition (Zaki 2013). Consistent to Bayesian approaches on physical perception (Ernst and Bulthoff 2004; Friston and Stephan 2007), the models state that the more cues converge over modalities, i.e. the stronger conditional probabilities ('minimized free energy'; Friston 2012), the stronger the emotional experience of the individuals (Zaki 2013) (see 1.4.3).

As can be seen in Figure 17, we have specified the role of convergence regions. However, we do not show how different convergence regions (which may operate on different hierarchical levels) interact with each other. According to Damasio (1989), convergence regions in sensory association cortices bind more basal perceptual features (e.g. the aSTG) and are likely to 'cooperate' with higher-order convergence regions, binding more abstract and semantic concepts (like e.g.

the TP). An examination of those interactions would be an interesting aim for future research on integration of multisensory socio-emotional cues for which the neurobiological model for cue-integration could provide a useful theoretical framework.

For episodic simulation, we have shown that mnemonic integration is instantiated in changes of connectivity between brain regions that are key for different memory types (aHP (AEM) and TP (SM))⁷. In addition, this connectivity follows a lateral specialization of the key regions across hemispheres (left aHP to right TP). The integration and coordination of activity from two hemispheres is a basic principle of brain function. The demonstration of hemisphere specific allocation to memory sub-function, however, is pretty progressive and points to the importance of inter-hemispheric interactions for advanced memory-based social cognition while it may also be related to its importance for beneficial social interactions and evolutionary viability. Neural propagation across hemispheres, between left HP and right TP is most likely conveyed via the anterior commissure (Catani und de Schotten 2012). Spherical deconvolution tractography has shown that the main commissural pathway, the corpus callosum, has absence or scarcity of projections to the anterior temporal lobe (aTL) in humans (Catani und de Schotten 2012). Even though the role of the anterior commissure is not well understood to date, it is suggested that it may be specifically responsible for inter-hemispheric transfer for this rostral pathway in the temporal lobe (Demeter et al. 1990). The importance of the anterior commissure as inter-hemispheric cross route was recently supported by a study showing that widespread inter-hemispheric functional connectivity remained intact in rhesus monkeys when sparing the anterior commissure from complete commissurotomy (O'Reilly et al. 2013). Future research addressing the role of the anterior commissure for socio-emotional cognition is highly requested.

Importantly, neural integration mechanisms operate also during absence of socio-emotional cues (dash dotted line in Fig. 17), i.e. internally driven cognition, most frequently measured in the fMRI scanner without an overt task during the so-called 'resting state'. Since episodic simulation occurs during both functional states, rest and task, we found the inter-hemispheric mechanism (left aHP-rightTP) during both resting state and task-based cognition consistent with Cole et al. (2014), who showed similarities between intrinsic and extrinsic connectivity. Nonetheless, the

⁷ For simplicity, only semantic and episodic memories are listed in the model. It is important to note that there are additional types of memory like for example procedural memory.

relation of the area above and below the dashed line bears tremendous examination for future research, specifically for social neuroscience (see 5.6).

The proposed neurobiological model seeks to provide a better understanding of neural integration of socio-emotional cues in the human brain. By showing interactions of integration mechanisms, it suggests a neural processing framework that can serve to generate future research questions. This is specifically important for psychiatric disorders with impairments in social and emotional functioning, which may be related to dysfunctional integration mechanisms and dysfunctional interactions. In this section, it has already been shown how this model can guide prospective research. Additional outstanding research questions are formulated in Table 3.

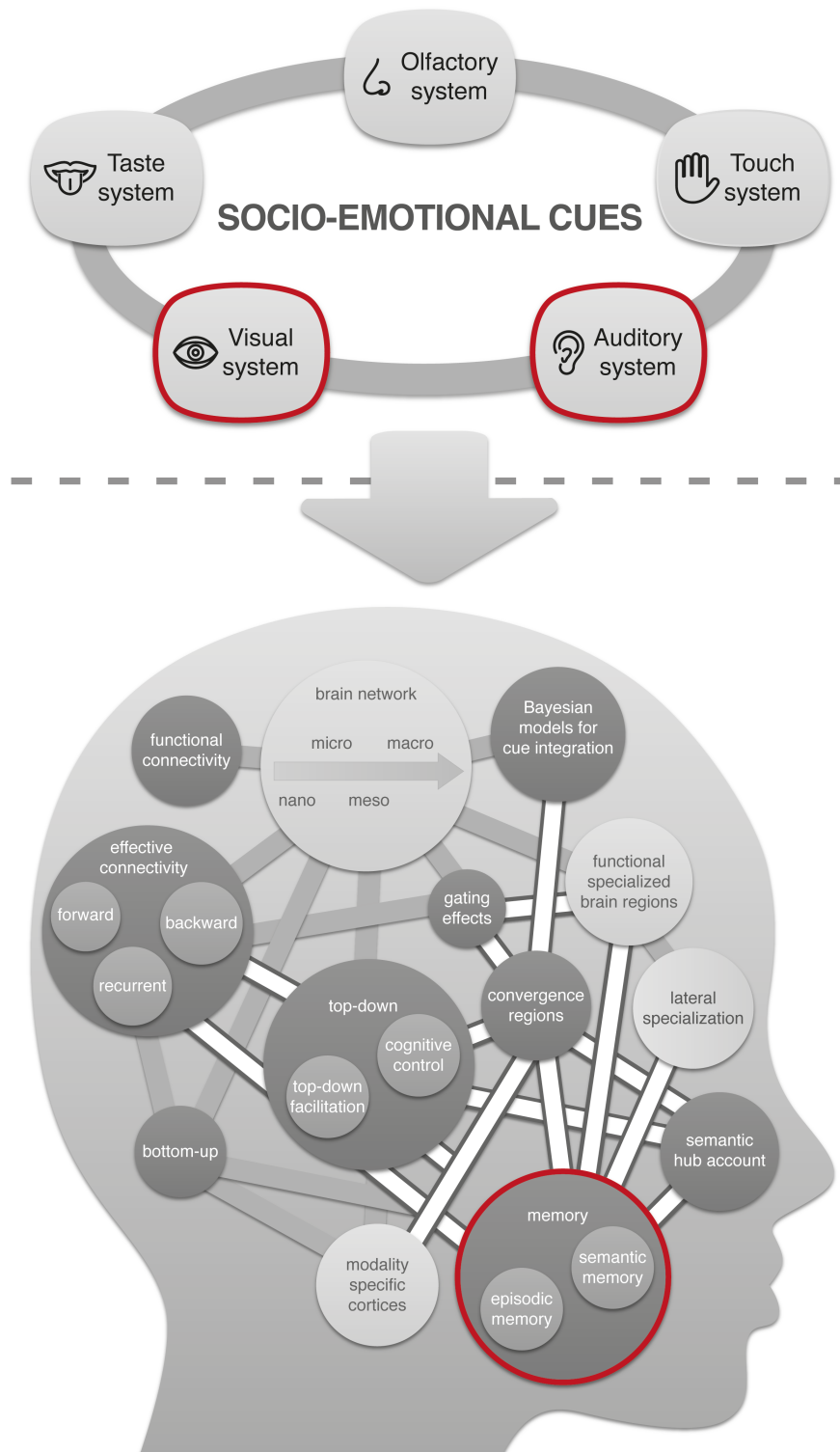


Figure 17 A neurobiological model of socio-emotional cue-integration.

Based on neurocognitive integration theories (1.3) integration mechanisms are represented inside the head and are linked and arranged according to the findings of this thesis. Socio-emotional cues were systematically manipulated (red circles) and specific findings of this thesis are highlighted with white connections. The dashed line separates the 'external' from the 'internal world'. For details, please refer to the main text (5.2).

5.4 The role of the temporal pole in social cognition

This thesis has substantially contributed in clarifying the role of the TP in social cognition. As portrayed in the Introduction (1.4.2), the TP is part of the mentalizing network (Frith and Frith 2003). It is part of the association cortex and involved in multimodal sensory integration (Damasio 1989; Olson et al. 2007; Skipper et al. 2011). The TP is located at the anterior tip of the temporal lobe (Brodmann's Area 38). It is strongly interconnected with the AMY (Nakamura and Kubota 1996; Stefanacci and Amaral 2002), with antecedent regions within the ventral visual stream and with the orbitofrontal cortex (OFC) via the longitudinal fasciculus (Crosby 1963; Catani et al. 2003).

Several pieces of evidences have been linked to different functions of the TP. Based on neurodegenerative disorders like SD for example, TP was implicated in SM and suggested to act as an amodal semantic hub (McClelland and Rogers 2003; Patterson et al. 2007). Cortical damage to either unilateral or bilateral aTL resulted in aberrant social behavior including hypoemotionality and hypersexuality. This was first observed in monkeys and was called the Kluver-Bucy syndrome (Kluver and Bucy, 1937), but was later also detected in humans. Mounting evidence since then has underscored the involvement of the TP in socio-emotional cognition and behavior (Olson et al. 2007, 2013; Wong and Gallate 2012).

The TP plays a prominent role in including language processing (Hickok and Poeppel 2007; Altmann et al. 2012), face processing (Jimura et al. 2009), emotion (Royet et al. 2000; Aust et al. 2013), empathic behavior (Rankin et al. 2006; Parkinson and Wheatley 2014) and social concepts (Zahn et al. 2007, 2009). Previous studies reported emotion effects of sad and fearful contexts for the processing of neutral social scenes and faces (Mobbs et al. 2006; Willems et al. 2011). Notably, the TP was associated with the retrieval of social knowledge. According to Frith and Frith (2003), the TP retrieves social knowledge on the basis of past (autobiographical) experiences as semantic frame for current perceptual input. In their seminal review article, Olson et al. (2013) suggest that TP mediates between perceptual input and biographical knowledge like for example names and biographies of people as well as social concepts and traits. Despite inconsistencies regarding TP's laterality differences (Wong and Gallate 2012), the right TP seems to be particularly involved in emotion processing (Olson et al. 2007). In a similar vein,

activation in the right TP has repeatedly been associated with better performance in theory of mind and empathy tasks (Völlm et al. 2006; Mier et al. 2010).

The thesis has supported the role of TP in socio-emotional cognition by showing an emotion effect of sad context and empathic concern in the right TP. This has advanced its role by showing the strong neuromodulatory impact of TP on other (perceptual and emotional) processing streams. We have therewith extended the idea of a semantic hub by stressing that TP is a semantic hub integrating multisensory information but might rather be a gateway between bottom-up and top-down processing for the integration of external socio-emotional cues. We have further specified the controversial laterality differences of TP by showing that the right TP is involved in integration of semantic with episodic memory as revealed by inter-hemispheric connections to the left aHP. Autobiographic events are highly personal and emotional, which is also supported by increasing aHP-activity as a function of vividness, emotionality and personal significance of AEM contents (Maguire and Mummery 1999; Addis et al. 2004; Binder et al. 2009). We therefore suggest that the right TP is more often reported in the context of emotion processing because of its function to integrate episodic memory, while the left TP might be more engaged when language processing is involved.

Indeed, the left TP is usually associated with name retrieval (Simmons et al. 2010; Tsukiura 2008, 2010), whereas the right TP is also associated with retrieval of episodic knowledge of familiar or famous faces (Blair et al. 1999; Dolan et al. 2000; Gainotti 2007a, 2007b; Leveroni et al. 2000). The right TP reliably responds to empathy and theory of mind tasks (Rankin et al. 2006; Wong and Gallate 2012; Ross and Olson 2010), when pairing a fearful sentence with a visual scene (Willems et al. 2011), processing of social (e.g. 'ambitious' 'honorable') vs. animal concepts (e.g. 'trainable' 'healthy') (Zahn et al. 2007; 2009) and for personally relevant compared to non-personal memories (Maguire and Mummery 1999), i.e. tasks, which require the integration of AEMs. Furthermore, psychological and socio-emotional problems are particularly pronounced in patients with damage to the right TP (Edwards-Lee et al. 1997; Glosser et al. 2000; Kipps et al. 2009; Thompson et al. 2003), which might rely on the disability to integrate AEMs.

The left TP, however, was found to be involved in verbal processing like learned name retrieval (Tsukiura et al. 2011) or processing of short narratives (Hasson et al. 2007; Ferstl and von Cramon 2007). Evidence for enhanced RSFC to

the temporo-sylvian language network for the left compared to the right TP reinforces its specialization for language (Hurley et al. 2015).

As mentioned above, the findings of this thesis have brought me to suggest a potential role of the TP as gateway between top-down and bottom-up processing. This idea can be linked to a framework by Mesulam (1998, 2000), who assigns brain regions along a transition of external to internal information processing (see also 5.6). According to this approach, sensory information from the environment is processed in unimodal primary sensory areas and association cortices in a bottom-up fashion and projected to areas leading to an internal processing state and characterized by activity in heteromodal association cortices and paralimbic regions, like e.g. TPs and insula. Brain areas engaged solely in the processing of internal information are according to Mesulam (2000) the hypothalamus and limbic regions (e.g. AMY, HP). Bottom-up connections of TP to orbitofrontal regions as well as top-down modulations of OFC to TP should be examined in the future (Table 3).

In Study 2, the comparison of sad against neutral context conditions and the parametric analysis revealed TP activations with regional overlap. However, the cluster responsive to empathic concern was located more medially and spread more posteriorly, whereas the cluster showing an emotion effect of sad context was located more anteriorly and laterally (Fig. 18). In most studies, the TP is treated as a homogenous region (BA38) with a unified function. Contradicting this view, a recent study has shown a connectivity-based parcellation of the TP in three distinct areas, which appear to be key for different processes (Fan et al. 2014). In line with this segregation, the emotion effect of sad context corresponds to the medial TP subregion, which is characterized by connections with emotion-related areas (Fan et al. 2014). Empathic concern, however, rather involves the lateral TP subregion, which shows strong positive correlations with the default mode regions (Fan et al. 2014), generally discussed to be involved in mentalizing and empathy (Schilbach et al. 2008; Mars et al. 2012). Consistently, the TP is part of the dorsomedial DN-subsystem, which is presumed to be involved in mental state inferences of self on others (Andrews-Hanna et al. 2014). The anatomical dissociation of TP in Study 2 might therefore indicate functionally specialized sub-regions as described by Fan et al. (2014).

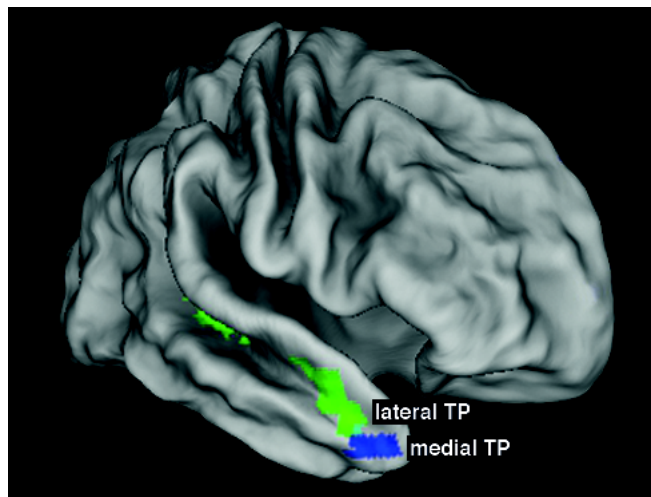


Figure 18 Anatomical dissociation of TP activation.

The emotion effect of sad context [sad context, film+music&sad context, film+no music] > [neutral context, film+music&neutral context, film+no music] (blue; $p < 0.05$, cluster extent 10) and the parametric effect of empathic concern (green: $p < 0.001$, cluster extent 30, FWE corrected at cluster-level) are superimposed on a 3D brain surface using the Caret5 software. The emotion effect (blue) corresponds to the medial TP and the parametric effect to the lateral TP (green) (cf. Fan et al. 2014).

5.6 A required internal-external reciprocity for social processing

As described in the Introduction section, the DN is mainly associated with an internal mental processing mode. The DN is increasingly recruited with decreasing external task demands and is anti-correlated with neural networks for exteroceptive processing like the dorsal attention system (Fox et al. 2005; Fransson 2005; Uddin et al. 2009). Consistently, DN activity is decoupled from sensory processing and inversely associated with task performance (Weissman et al. 2006; Kam et al. 2011).

However, the orthogonal relation of exogenous and endogenous processing networks has been questioned as methodological artifact of spuriously induced anti-correlations by global signal regression (Murphy et al. 2009). In addition, mind wandering can be integrated into executive models of attention. The DN is recruited during multiple tasks like the generation of new ideas (Ellamil et al. 2012), social working memory (Meyer et al. 2012), processing of self and others (Uddin et al. 2007; Qin and Northoff 2011), theory of mind (Gallagher and Frith 2003; Saxe and Kanwisher 2003), semantic processing and integration of context information (Fairhall and Caramazza 2013; Hasson et al. 2008) as well as immersion during film viewing (Golland et al. 2007). Hence, the DN is recruited during tasks that require internal mental operations, mostly with a social nature involving self-reflection.

An internal and an external processing mode interact (fluctuate) regularly during everyday experiences (Binder et al. 1999; Smallwood et al. 2008) for which different switching-mechanism are proposed. Those are for example the phase synchronization as measure for neural integration within networks (Varela et al. 2001; Ward 2003), the ventral attention system, i.e. mainly right temporoparietal junction (TPJ) and right inferior frontal gyrus (IFG) (Corbetta and Shulman 2002; Corbetta et al. 2008, Weissman et al. 2006), right fronto-insular cortex (Sridharan et al. 2008; Menon and Uddin 2010) or cortical midline hubs (Fox et al. 2006a; Smallwood et al. 2013). In an fMRI study of Spreng et al. (2010b), it was found that a frontoparietal control network flexibly couples with the DN and with dorsal attention network to mediate goal-directed cognition.

A new framework suggests that processing demands mediate a coordinated interplay of internal and external processing modes. Accordingly, co-occurrence and cooperation between processing modes is possible to the extent that both require a balanced amount of cognitive load and attention demands (Dixon et al. 2014). Real-life social interactions and social cognition tasks (with socio-emotional cue-

integration) might be an excellent case of mutual cooperation of internal and external processing modes. Social interactions demand the combination of external socio-emotional processing like language, facial expressions and biological motion with internal socio-emotional cues like attending to one's own feelings and drawing inferences on others' mental states. Social deficits in psychiatric disorders might represent an imbalance of switching between internal and external processing (Kennedy et al. 2006). In line with this, socially anxious individuals are characterized by increased self-focused attention and a hyperactivation of DN regions (Boehme et al. 2015). Training to switch between inward and outward attention could have therapeutic relevance and should be investigated in future studies. Study 3 of this thesis showed that crossed-hemispheric connectivity of left aHP and right TP is at the core of episodic simulation in a social context and has equally been observed during rest and during task. For social cognition, this thesis therefore suggests to study internally and externally driven brain organization within a unified framework.

An internal-external reciprocity is further supported by a strong correspondence between intrinsic and extrinsic network architectures. Cole et al. (2014) have recently compared functional connectivity during rest and multiple tasks (social, emotional, n-back, motor etc.) and revealed striking overlap irrespective of task using two independent data sets. Overall, the intrinsic brain architecture is conceived as a standard state of brain function, which shapes and prepares extrinsic (task-induced) network architectures and replays extrinsic activity during rest (Fox et al. 2006b; Vincent et al. 2006; Smith et al. 2009; Raichle et al. 2010; Cole et al. 2014; Deco and Corbetta 2011; Hartzell et al. 2014).

5.5 The importance of memory for social cognition

“Memory connects innumerable single phenomena into a whole, and just as the body would be scattered like dust in countless atoms if the attraction of matter did not hold it together so consciousness – without the connecting power of memory – would fall apart in as many fragments as it contains moments.”

Ewald Hering, 1870

This quote by Hering (1870) in Vienna establishes the relationship between memory and consciousness and thus accentuates the importance of memory functions for all phenomena that are related to social cognition and social behaviors. In their seminal review, Schacter et al. (2012) have described that memory functions are not only related to the past but importantly also to imagination of the future while recruiting the

same brain regions (see also Buckner and Carroll 2007; Buckner 2010). In addition, there is a broad overlap of the network engaged when retrieving personal events and the mentalizing network (Rabin et al. 2010). Also Spreng et al. (2009, 2010a, 2012) have reported brain activity in DN for a variety of memory-based cognitive domains like autobiographical remembering, prospection and theory of mind. In a Study by O'Callaghan et al. (2015), internal mental activity related to memory-based construction/simulation was associated with temporopolar-hippocampal functional connectivity. The question, however, whether there is a discrete social memory system is still unresolved.

Some studies have directly linked memory processes and social cognition. Meyer et al. (2012, 2015) have found brain activity that was exclusively related to social working memory demands and at the same time mirrored perspective-taking abilities of the participants. In a similar vein, brain activity in the DN was involved in the integration of social and personality information when predicting future behaviors of other people (Hassabis et al. 2014). Yang et al. (2013) found that the use AEM during social processing was associated with stronger coupling of DN regions, specifically in medial temporal lobe (MTL) structures including the hippocampus (HP). An important line of research follows the same route and has examined the impact of episodic memory retrieval on the ability to put oneself into the shoes of another person. Study 3 of this thesis for example investigated this question. Perry et al. (2011) have shown that people use their own experiences to understand others. Specifically the HP was associated in emotional judgments of others and its activity was predicted by how similar the participants felt with the individuals. Therefore, the authors suggested the HP to serve as a modulator for empathic responses. Ciaramelli et al. (2013) also found a modulating effect of memory on empathic responses: Knowledge about which situations characters experienced in the past significantly influenced the participants' empathy towards the characters when they encountered a similar situation, in line with the episodic simulation hypothesis (see 1.3.5).

A recent paper has shown that the HP is involved in the construction of an abstract geometric representation of social relationships (Tavares et al. 2015). The left HP was the main brain structure that tracked the relationship to virtual characters in a two-dimensional space in relation to power (e.g. competence, dominance, hierarchy) and affiliation (e.g. warmth, intimacy, trustworthiness). Importantly, activity in HP was positively correlated with the individuals' social skills, again stressing the

importance of episodic memory (in HP) for social cognition. The link of AEM and social cognition was also shown by Study 3 of this thesis demonstrating the beneficial effect of using one's own experiences (AEM) to infer others' mental state. This result has led to the assumption that a hippocampal dysfunction or more specifically, a dysfunctional mnemonic integration with disrupted left aHP to right TP connectivity, may contribute to maladaptive empathic abilities in psychiatric diseases. In correspondence with this idea, one study (Pantazatos et al. 2013) has correspondingly shown reduced hippocampal-temporopolar functional connectivity as a biomarker for diagnoses of social anxiety disorder. This feature disappeared after 8 weeks of treatment with the selective serotonin reuptake inhibitor (SSRI), paroxetine concomitant with a decrease of symptom severity (Pantazatos et al. 2013).

The results of Tavares et al. (2015) are also remarkably in line with the QT's outline of the hippocampal system as most important for attachment related affects. The thesis' comment on the QT proposes a dysfunctional mnemonic integration, impaired access to memory content and reduced top-down modulations as biomarker for ASD. Linking hippocampal function to the dimension of affiliation when constructing an abstract social space (Tavares et al. 2015) may shed more light on the attachment related hippocampus-centered affect system as described by the QT.

Taken together, future empirical and conceptual neuroscientific inquiry should not only consider an internal-external reciprocity but should essentially investigate memory processes that enable social cognition.

5.7 Conclusions and future directions

This dissertation has investigated neural network dynamics during socio-emotional cue-integration by systematically manipulating cues with regard to their multisensory composition. The results have motivated a neurobiological model for socio-emotional cue-integration offering a scheme, which links integration mechanisms and their interactions. Based on this model, a real-life socio-emotional experience can be conceived as the result of interacting mechanisms, while impairments in social and emotional functioning can be conceived as a dysfunctional interaction. The thesis provided evidence for multisensory convergence regions operating at different hierarchical levels (e.g. aSTG and TP). It has advanced the concept of convergence regions by showing their neuromodulatory impact on visual to emotional processing streams. The thesis placed TP at the core of social cognition with a critical role in exerting top-down modulations as a function of task demands in line with top-down

facilitation models, which is why it was suggested to act as gateway between top-down and bottom-up processing. The thesis further specified the lateral specialization of the right TP in integrating episodic memory provided by the hippocampal system and thus elucidated previous reports of the right TP in emotion processing (Olson et al. 2007). The thesis suggests a promising future avenue for research on social cognition, which is to study brain organization as an internal-external reciprocity and to focus on memory processes as modulating factor for socio-emotional abilities.

TABLE 3 OPEN QUESTIONS.

A set of research questions raised by the neurobiological model of socio-emotional cue-integration and broader questions addressing social cognition research in general

1. Future studies should examine the top-down influence of higher-order prefrontal areas on mnemonic integration of semantic with episodic memory, namely how prefrontal areas like the OFC exert control on the connectivity from HP to the TP. This could be achieved by adding a behavioral component to the experiment and by means of nonlinear dynamic causal modeling (DCM).

2. The possible role of the TP as a gateway between top-down and bottom-up processing should be examined in more detail. Specifically whether the TP not only exerts top-down modulations to lower level perceptual areas, but also provides bottom-up perceptual information to higher order cognitive areas, as indicated for example by functional connectivity to the orbital PFC (Kahnt et al. 2012). The prominent co-activation of the TP and the IFG also needs to be elucidated in more depth.

3. The findings that led to a neurobiological model of socio-emotional cue-integration, should be substantiated by combinations of functional and structural connectivity analyses. The inter-hemispheric mechanism for episodic simulation for example could be specified with regard to its reliance on fiber strength of callosal connections, particularly in patient groups with impaired socio-emotional functioning.

4. Social deficits in mental illnesses might represent an imbalance of switching between internal and external processing (Kennedy et al. 2006). Consistently, socially anxious individuals are characterized by increased self-focused attention and a hyperactivation of DN regions (Boehme et al. 2015). Training to switch between inward and outward attention could have therapeutic relevance and should be investigated in future studies.

5. A recent development is that ordinary social interactions occur more often in the social media like *facebook* or *instagram*. The important characteristic is that naturalistic socio-emotional cues are almost lacking entirely. Social interactions get more cognitive and abstract and less real, which is observable in neural correlates (Meshi et al. 2013). The advance of virtual realities particularly also in Asia (cf. the major Chinese video-based social network with over 300 million users: *YY.com*) change our social lives and our 'social brains' and bears examination in future research.

6. Mentalizing is mostly investigated with its capacity to increase prosocial behavior. However, understanding what another person thinks and feels is not always used in the other's favor. Some examples are sadism, torture and the abuse of power (e.g. Milgrim experiment and Stanford prison experiment). In addition to the prosocial aspects of empathy that were examined in the present studies, intense empirical and conceptual neuroscientific inquiry on the 'evil mentalizing' is highly warranted.

7. In the present thesis movie clips are used to parallel real-world perception. However, passive viewing paradigms investigate social cognition still from an observer-perspective in contrast to a participator-perspective. In this context, film stimuli could also be labeled seminaturalistic. The claim of a second person neuroscience (Schilbach et al. 2013) should be used as a model to examine the modulatory impact of socio-emotional cues on neural network dynamics in real-world scenarios.

8. In Project 4 we discussed impaired cue-integration in ASD based on atypical perceptual integration, reduced prefrontal large-scale connectivity (Shalom 2009) and the theory of weak central coherence (i.e. lack of holistic processing, Frith and Happé 1994) suggesting ASD to be a neurocognitive integration disorder. These hypotheses should be tested in future research and extended to other psychiatric illnesses with impairments in social functioning such as depression and schizophrenia.

9. The neurobiological model of socio-emotional cue-integration depicts neural mechanisms underlying an internal processing of external information (inside the head). This integration is notably characterized by a striking inter-individual difference. Future studies should focus on these differences and link those to specific mechanisms.

10. The application of advanced methods for investigation of effective connectivity within large-scale brain networks (e.g. advanced developments of graph analysis and computational models) as well as multimodal imaging may help to complement the tentative neurobiological model of socio-emotional cue-integration in the future.

11. The neurobiological model of socio-emotional cue-integration is a cognitive model and should be extended by a behavioral component, specifically how cue configuration changes activity measured empirically (e.g. prosocial behavior acquired by the amount of donations etc.).

12. The importance of memory processes and simulation accounts in social cognition is stressed in Study 3 by highlighting the impact of using one's own experiences to empathize with others. This has implications for patient populations with empathic deficits, such as ASD. To prompt individuals to relate to self-referential experiences when trying to understand others may have therapeutic benefits and should be examined in more detail.

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Supplements

A Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,

dass ich mich nicht bereits anderwärts um einen Doktorgrad beworben habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze und

dass ich die zugrunde liegende Promotionsordnung vom 02.12.2008 kenne.

Berlin, den 30.06.2015

Corinna Pehrs

B Research articles

Project 1

Pehrs C, Deserno L, Bakels JH, Schlochtermeyer LH, Kappelhoff H, Jacobs AM, Fritz T, Koelsch S, Kuchinke L. 2014. How music alters a kiss: superior temporal gyrus controls fusiform–amygdalar effective connectivity. *Soc Cogn Affect Neurosci.* 9:1770-1778.

Abstract

While watching movies, the brain integrates the visual information and the musical soundtrack into a coherent percept. Multisensory integration can lead to emotion elicitation on which soundtrack valences may have a modulatory impact. Here, dynamic kissing scenes from romantic comedies were presented to 22 participants (13 females) during functional magnetic resonance imaging scanning. The kissing scenes were either accompanied by happy music, sad music or no music. Evidence from cross-modal studies motivated a predefined three-region network for multisensory integration of emotion, consisting of fusiform gyrus (FG), amygdala (AMY) and anterior superior temporal gyrus (aSTG). The interactions in this network were investigated using dynamic causal models of effective connectivity. This revealed bilinear modulations by happy and sad music with suppression effects on the connectivity from FG and AMY to aSTG. Non-linear dynamic causal modeling showed a suppressive gating effect of aSTG on fusiform–amygdalar connectivity. In conclusion, fusiform to amygdala coupling strength is modulated via feedback through aSTG as region for multisensory integration of emotional material. This mechanism was emotion-specific and more pronounced for sad music. Therefore, soundtrack valences may modulate emotion elicitation in movies by differentially changing preprocessed visual information to the amygdala.

due to copyright reasons, this paper is not included in the online version.

<http://dx.doi.org/10.1093/scan/nst169>

Project 2

Pehrs C, Zaki J, Schlochtermeyer LH, Jacobs AM, Kuchinke L, Koelsch S. 2015. The temporal pole top-down modulates the ventral visual stream during social cognition. *Cereb Cortex*. [Epub ahead of print].

Abstract

The temporal pole (TP) has been associated with diverse functions of social cognition and emotion processing. Although the underlying mechanism remains elusive, one possibility is that TP acts as domain-general hub integrating socioemotional information. To test this, 26 participants were presented with 60 empathy-evoking film clips during fMRI scanning. The film clips were preceded by a linguistic sad or neutral context and half of the clips were accompanied by sad music. In line with its hypothesized role, TP was involved in the processing of sad context and furthermore tracked participants' empathic concern. To examine the neuromodulatory impact of TP, we applied nonlinear dynamic causal modeling to a multisensory integration network from previous work consisting of superior temporal gyrus (STG), fusiform gyrus (FG), and amygdala, which was extended by an additional node in the TP. Bayesian model comparison revealed a gating of STG and TP on fusiform–amygdalar coupling and an increase of TP to FG connectivity during the integration of contextual information. Moreover, these backward projections were strengthened by emotional music. The findings indicate that during social cognition, TP integrates information from different modalities and top-down modulates lower-level perceptual areas in the ventral visual stream as a function of integration demands.

due to copyright reasons, this paper is not included in the online version.

<http://dx.doi.org/10.1093/cercor/bhv226>

Project 3

Manuscript

1 Research Article

2

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4 **Hippocampal-Temporopolar Connectivity Contributes to**

5 **Episodic Simulation during Social Cognition**

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33 Keywords: default network | dynamic causal modeling | hippocampus | lateral

34 specialization | memory | resting state functional connectivity | temporal pole

35 **Abbreviations**

36 AEM, autobiographic episodic memory; aHP, anterior hippocampus; AMY,
37 amygdala; BMS, Bayesian model selection; BOLD, blood-oxygen- level
38 dependent; DCM, dynamic causal modeling; DN, default network; EPI, echo-
39 planar imaging; fMRI, functional magnetic resonance imaging; FWE, family-wise
40 error; LI, laterality index; MTG, middle temporal gyrus; PCC, posterior cingulate
41 cortex; PE, parameter estimates; ROI, region of interest; RSFC, resting state
42 functional connectivity; SEM, standard error of the mean; SM, semantic memory;
43 SPM, statistical parametric mapping; SSRI, selective serotonin reuptake
44 inhibitor; STG, superior temporal gyrus; TBEC, task based effective connectivity;
45 TP, temporal pole; TPJ, temporoparietal junction

46 Abstract

47 Using one's own experience to understand another person's mind is fundamental
48 for empathic concern. However, interactions of memory systems underlying
49 these processes are only poorly understood. During episodic simulation, context-
50 dependent autobiographic episodic memory (AEM) is integrated with context-
51 independent semantic memory (SM). This study maps mnemonic integration
52 onto the connectivity of two brain regions, which are key for AEM and SM, the
53 anterior hippocampus (aHP) and the temporal pole (TP). Brain activity was
54 measured during resting state and task state in the same set of participants,
55 using fMRI. The task contained empathic film clips, half of which were preceded
56 by written context information. Contexts triggered episodic simulation by
57 describing the character's situation and were found to increase the participant's
58 empathic concern. Seed-based resting state functional connectivity analyses
59 revealed a distinct crossed-hemispheric coupling of left aHP and right TP. Task-
60 based effective connectivity using dynamic causal modeling (DCM) on a 8-region
61 network including both left and right hemispheric aHPs and TPs revealed
62 stronger effective connectivity from left aHP to right TP as a function of context
63 information and episodic simulation. Together, our findings demonstrate a
64 unique crossed-hemispheric mechanism as neural basis for episodic simulation.
65 They establish a novel perspective on TP function with lateral specialization of
66 the right TP to integrate episodic memory and shed new light on its widespread
67 associations with emotion processing. The study is the first to suggest that
68 episodic simulation is based upon neural integration of brain regions specialized
69 for different memory types and located in different hemispheres. Our results

70 indicate that inter-hemispheric interactions are crucial for advanced memory-
71 based social cognition. The retrieval of self-referential episodic memory was
72 proven as highly beneficial for empathic responses, suggesting a putative
73 impairment of this mechanism in psychiatric diseases with deficits in socio-
74 emotional processing such as autism spectrum disorder.

75

76 **Introduction**

77 Memory processes are essential functions during social cognition [1]. Episodic
78 simulation, for example, refers to the use of autobiographic experiences to
79 understand current events or future scenarios. In a social context, it enhances
80 prosocial orientation by increasing perspective taking capabilities [1,2].
81 Correspondingly, the episodic simulation hypothesis states that people use own
82 experiences to simulate others' thoughts and feelings [3-5]. Retrieving similar
83 situations from one's past promotes the capacity to feel with and understand
84 another person [6-8] and may thus be necessary for successful real-world social
85 interactions.

86 **Episodic simulation requires the integration of semantic with episodic** 87 **memory**

88 In a previous study, we showed that context information to a characters'
89 situation in a movie clip increases the participant's empathic concern [9]. For
90 example, a brief text (preceding movie clips) provided information about a
91 recent loss of a loved person, and had the potential to reactivate prior
92 experiences in the participants [10]. The increase of empathic concern was
93 associated with activations in the right temporal pole (TP), and anterior
94 hippocampus bilaterally (aHP) (Fig 1A.2 (bottom)). This result is consistent with
95 the notion that cognitive operations of episodic simulation are dynamic
96 interactions of different memory systems. Context-dependent prior experiences,
97 i.e. autobiographic episodic memory (AEM), are integrated with context-
98 independent general knowledge, i.e. semantic memory (SM) [11]. General

99 knowledge is necessary to understand a person's momentary situation (e.g.
100 knowing what a breakup is), while retrieving episodic memory from
101 autobiographic experiences (a self-involved breakup) helps to improve that
102 understanding.

103 Although both memory systems (AEM and SM) are closely linked [12-14]
104 and interdependent [15,16], neuropsychological as well as neuroimaging
105 research has shown a dissociation of cortical regions preferably engaged in AEM
106 or SM [15,17].

107 **Hippocampal-temporopolar connectivity reflects mnemonic integration**

108 Based on findings from semantic dementia showing that neurodegenerative
109 atrophy in the anterior temporal lobe is associated with domain-general loss of
110 semantic knowledge [18-20], the TP is implicated in SM [21-24]. Processing of
111 AEM, by contrast, is associated with the hippocampus (HP) [25-29]. Seminal
112 studies directly comparing processing of AEM against processing of SM point to a
113 unique involvement of HP in AEM [14,28,29]. Regarding laterality differences, a
114 particular recruitment of the left HP for the retrieval of AEM is suggested [25,28-
115 31], whereas the right posterior HP appears to be preferentially involved in
116 spatial memory [17,28,30,32,33]. Mounting evidence now indicates a functional
117 segregation along the longitudinal axis, in which the anterior HP (aHP) is
118 predominantly involved in social and emotional memory [34-38], whereas the
119 posterior HP is engaged in more cognitive functions such as spatial memory
120 [32,33]. In line with the notion that AEM is closely related to emotion [6], there is
121 a preferential involvement of the aHP in AEM [39-41]. This is also supported by
122 increasing aHP activity as a function of vividness, emotionality and personal

123 significance of AEM contents [42-44]. Together, the findings point to a particular
124 involvement of the left anterior hippocampus in the processing of
125 autobiographic episodic memory.

126 The TP, on the other hand, is key to amodal semantic processing, and acts
127 as a convergence region [45] integrating sensory information from different
128 modalities [9,22,46]. The TP is implicated in various functions like the
129 processing of language [47], faces [48] and social concepts [49] as well as
130 empathic behavior [50] and emotion [51-53]. With regard to laterality
131 differences, the right TP seems to be more strongly involved in semantic
132 processing with emotional content [46,54]. According to Frith and Frith [55] the
133 TP is part of the mentalizing network and retrieves social knowledge on the
134 basis of past (autobiographical) experiences as semantic frame for current
135 perceptual input, and might thus be necessary for episodic simulation.

136 **The present study - Hippocampal-temporopolar connectivity during**
137 **internally and externally driven episodic simulation**

138 Episodic simulation was previously examined as unified concept [2,56], while
139 the underlying interaction of different memory sub-systems was rarely
140 addressed (but see [57]). Moreover, an investigation of SM with AEM integration
141 in the TP offering a brain mechanistic account including laterality differences is
142 lacking to date. We here address this unresolved question by mapping SM and
143 AEM processing on the connectivity of two key structures, the TP and the aHP,
144 specialized for SM and AEM, respectively. For this purpose, two experiments
145 were performed in the same sample of 28 healthy participants (see Fig 1A.1,
146 1A.2).

147 In Experiment 1, brain activity of the participants was measured during
148 resting state in the fMRI scanner (Fig 1A.1). Mental operations during rest are
149 strongly associated with social processing [58,59] and episodic simulation [60-
150 63]. Experience sampling revealed that, during rest, individuals engage in self-
151 referential mentation about imagining/planning the future, inferring mental
152 states of others, current concerns and reflecting about social interactions
153 [64,65], processes for which memory content is used in a constructive manner.
154 This thought activity is suggested to be underpinned by a distributed set of brain
155 regions, referred to as the default network (DN), with the TP and HP being part
156 of the so-called extended DN [66,67]. We conducted a resting state functional
157 connectivity analysis (RSFC, i.e., intrinsic correlations between activity of brain
158 areas in the absence of overt stimulation or task demands) [68] to examine TP-
159 HP connectivity including laterality differences placing the seed regions in
160 bilateral TPs (Fig 1A.1, 1B.1).

161 In Experiment 2, a task state was induced by the presentation of empathy-
162 evoking film clips that were preceded by varying context information provided
163 by short written texts with either a neutral or sad content (Fig 1A.2) (details in
164 [9]). The first condition (Fig 1A.2, 1) was a control condition showing a fixation
165 cross, followed by a silent film clip without preceding context (“no context”
166 condition = film only). The second condition (Fig 1A.2, 2) started with a neutral
167 context followed by a fixation cross and a silent film clip (“neutral context”
168 condition = neutral context, film + no music). The third condition (Fig 1A.2, 3)
169 started with a sad context followed by a fixation cross and a silent film clip (“sad
170 context” condition = sad context, film + no music). Three further conditions (Fig
171 1A.2; conditions 4-6) also arose from the three different context conditions

172 (no/neutral/sad context), but included sad music played during the presentation
173 of the film clip. The sad context described people suffering from plights, like for
174 example a recent loss of a loved person. The neutral context was created in
175 describing the general set-up, in which the character is presented in the clip (e.g.
176 sitting in a car, drinking a glass of water). The presence of a contextual framing
177 (sad and neutral) was sought to trigger episodic simulation by retrieving
178 previous experiences from memory [10].

179 Dynamic causal modeling (DCM) was applied to examine changes in
180 effective connectivity between TP and aHP as a function of context and episodic
181 simulation. A set of 15 models was fitted to the data, each assuming different
182 modulatory input on TP-HP connections within and across hemispheres (Fig
183 1B.2). The models were stratified in 3 model families with forward connections
184 (TP to aHP), backward connections (aHP to TP) or recurrent connections (in
185 both directions) to determine the direction of AEM with SM integration.

186 Note that we evoked both internally (Experiment 1) and externally
187 (Experiment 2) driven states in the same participants (Fig 1A.1, 1A.2). This
188 allowed us to directly compare brain organization of two functional states,
189 whose underlying neural networks are suggested to act in opposition [69]. The
190 combination of two different connectivity methods, i.e. RSFC and task based
191 effective connectivity (TBEC) is a unique advance compared to previous research
192 in social neuroscience, where usually one state was examined in isolation. In
193 contrast to previous findings showing state-dependent differences for
194 connectivity of the human motor system [70], we hypothesized that both
195 experiments would show similar results. This assumption was based on the
196 cognitive processes of interest, which are inferences about others' mental state,

197 known to take place during both, task and resting state. Therefore, we
198 hypothesized a particular crossed-hemispheric connectivity between right TP
199 and left aHP across experiments assuming that episodic simulation, i.e.
200 interactions of memory systems, is mediated by the lateral specialization of the
201 key structures involved. A validation of our hypothesis would support the role of
202 TP in the retrieval of social knowledge during mentalizing as stated by Frith and
203 Frith [55] and would specify the role of the TP in terms of its likely function to
204 integrate episodic memory. Moreover, it would join resting state and task-based
205 brain organization into a unified framework.
206

207 **Fig 1. Timeline of experiments, fMRI results from a previous study [9] and**
208 **analyses of TP-HP connectivity.**

209

210 A: The same participants (henceforth referred to as Berlin sample) underwent
211 the measurement of fMRI data during 8 min of resting state (fixation cross, eyes
212 open) (A.1), followed by 51.67 min of a social cognition task (A.2), in which the
213 presentation of empathic film clips was varied by the factors music (off/on (blue
214 background)) and written context information preceding the film clips. The
215 context information was either neutral (green) or sad (red). Thus, there were six
216 conditions and a control condition with music only (A.2, 7). After the film clips
217 the participants rated their emotional experience in terms of *being moved* and
218 *compassion* on a 7-point Likert-scale (1 *not at all*, 7 *very much*). A parametric
219 modulation analysis from a previous study [9] with compassion ratings revealed
220 activations in bilateral anterior HP and right TP (A.2 (bottom)) suggesting
221 episodic simulation as cognitive process underlying an increase of empathic
222 concern for the movie characters. B: To investigate the contribution of TP-HP
223 connectivity to episodic simulation, a functional connectivity analysis was
224 applied to resting state data (B.1) by looking for correlations of the fMRI time
225 series of bilateral TP with each voxel in the rest of the brain. TP-HP effective
226 connectivity was examined during task using dynamic causal modeling (DCM).
227 This analysis tested the hypothesis that TP-HP connectivity changes as a function
228 of context information and episodic simulation (see Modelspace Fig 4).

229

230 **Results**

231 **Experiment 1 – Resting state functional connectivity (RSFC)**

232

233 Consistent with its presence in the DN, left and right TP showed RSFC to main DN
234 regions, namely the medial prefrontal cortex (mPFC), posterior cingulate cortex
235 (PCC), as well as temporo-parietal junction (TPJ), and to the extended DN,
236 namely middle temporal gyrus (MTG) and the TP bilaterally ($p < 0.05$, whole-
237 brain FWE-corrected, cluster extent > 10 voxels; Fig 2A.1, S1 Table). In
238 distinction to the left TP, the right TP showed additional functional connectivity
239 to aHP bilaterally and to the right Amygdala (Fig 2A.2; S1 Table).

240 A region of interest (ROI) analysis for HP was conducted using a map of t-
241 statistics containing the connectivity pattern from TP bilaterally. Averaged
242 individual parameter estimates (PE) within a 10mm sphere around individual
243 peaks within anatomical masks of the HP taken from the WFU Pick Atlas toolbox
244 [71,72] show significantly stronger connectivity of left and right HP to the right
245 TP than to the left TP (p 's < 0.05) (Fig 3A). This is a remarkable result
246 considering the fact that ipsilateral connectivity is generally stronger than
247 contralateral connectivity and emphasizes the strong cross-hemispheric
248 coupling of right TP and left HP.

249 The results were substantiated by identical analyses in another
250 independent data set of 198 participants (henceforth referred to as Cambridge
251 sample), taken from the freely accessible database “1000 Functional
252 Connectomes Project” (http://www.nitrc.org/projects/fcon_1000/) [73]. RSFC
253 to bilateral aHP was more pronounced for the right TP (Fig 2B.2, S2 Table).
254 Averaged individual parameter estimates (PE) show significantly higher

255 connectivity of left and right HP to the right TP than to the left TP (p 's < 0.001)
256 (Fig 3B).

257 To quantify laterality differences of TP-RSFC, weighted laterality indices
258 (LI_ws) were calculated for the Berlin sample within symmetric bilateral masks
259 for our key regions (TP and aHP) and for the DN consisting of PCC, mPFC, TPJ,
260 MTG, aHP and TP (for details see S1 Text) [74,75]. LI's quantify relative
261 differences in left versus right hemisphere activations. LI_w values lie on a
262 continuum between +1 (only left) and -1 (only right). The threshold for
263 hemispheric lateralization was > ±0.2, as in previous studies [74].

264 The results revealed a right lateralization of TP-RSFC to the DN (-0.36 ±
265 0.02(se)) and TP (LI_w mean -0.38 ± 0.02(se)), but a left lateralization for aHP
266 (0.25 ± 0.08(se)) (S1 Fig). These findings are consistent with a previously
267 reported right lateralization of DN regions associated with the frequency of mind
268 wandering [76,77]. In addition, a right-lateralization of the ventral attention
269 system, implicated in internally directed cognition, is reported [78].

270

271 **Fig 2. Resting state functional connectivity (RSFC).**

272 A.1: Connectivity pattern of left TP seed (see yellow ellipse in top left panel)
273 superimposed on left (L) lateral, medial, dorsal, and right (R) lateral, medial,
274 dorsal views and on coronal, sagittal and transaxial brain sections (below). A.2:
275 Connectivity pattern of the right TP seed; red arrows indicate RSFC to aHP
276 bilaterally. B.1: Same analyses in an independent data sample (Cambridge
277 sample, n = 198) showing the connectivity pattern of left TP, superimposed on
278 the same coronal, sagittal and transaxial brain sections. B.2: RSFC of the right TP
279 seed in the Cambridge sample. Coordinates on the bottom refer to MNI space. T-

280 maps of resting-state connectivity are thresholded at $p < 0.05$, whole-brain FWE-
281 corrected, cluster extent threshold $k > 10$ voxels.

282

283 **Fig 3. ROI analysis of HP.**

284 Sagittal (left), coronal (middle) transaxial (right) sections depicting HP-ROI
285 (green) taken from the anatomic labeling atlas (AAL) [79]. Coordinates refer to
286 MNI space. Bar plots depict averaged parameter estimates within a 10mm
287 sphere around individual peaks within left and right HP-ROIs of the Berlin
288 sample ($n = 28$) (A) and Cambridge sample ($n = 198$) (B). Error bars represent
289 standard error of mean.

290

291

292 **Experiment 2 – Task based effective connectivity (TBEC)**

293

294

295 In Experiment 1, resting state functional connectivity (RSFC) analysis has shown
296 a coupling of the right TP and HP bilaterally. This indicates a co-activation of
297 both regions during rest. For the analysis of TBEC, we used dynamic causal
298 modeling (DCM). In contrast to RSFC, TBEC aims to test how temporopolar-
299 hippocampal connectivity changes (decreases or increases) as a function of
300 context information to empathic filmclips (Fig 1B.1, B.2).

301 This analysis was motivated by the results of RSFC and the results of our
302 previous study [9] showing that the context information significantly increased
303 the participants' experience of compassion and was associated with responses in
304 the right TP, right aHP and left aHP (Fig 1A.2 (bottom), S1 Text, S3 Table).

305 A set of 15 models, each containing different bilinear modulations (by
306 context) on the four TP-HP connections, was created (Fig 4). An 8-region DCM

307 model including both left and right hemispheric regions with inter-hemispheric
308 interactions allows assessing all left and right connectivity parameters
309 (endogenous, driving and bilinear) over the same model space. The direction of
310 neural propagation from TP to aHP was tested by means of model families (Fig
311 4B, 4C, 4D) (for details on modelspace see *Methods and Materials*).

312 Random-effects family-based inference comparing backward, forward
313 and recurrent families revealed that the backward family (aHP to TP) clearly
314 outperformed the forward and the recurrent family with an exceedance
315 probability (EP) of 66.44% (Fig 5). The subsequent model comparison within the
316 backward family reveals the most plausible model with backward projections
317 from left aHP to right TP with an EP of 68.56%, compared with exceedance
318 probabilities of $\leq 8.6\%$ for all of the 14 models of the comparison (Fig 5). The
319 winning model structure indicates that context information determines the
320 neural propagation from left aHP to right TP. Consistent with our hypothesis and
321 with the results of RSFC, the TBEC analysis strikingly corroborates a coupling of
322 left aHP and right TP during episodic simulation. For inspections on parameter
323 estimates see S1 text, S4 Table and S5 Table.

324
325

326 **Fig 4. DCM Modelspace.**

327 A: Basic model structure depicting all nodes of the bilateral symmetric network
328 with driving input on V1 and STG (short arrows) and bilinear modulations
329 between aHP and TP (long arrows). B: Model-subspace showing all possible
330 variations of bilinear modulations with recurrent connections. These 15 models
331 were additionally modeled in a subspace with forward connections (C, from TP

332 to aHP) and a subspace with backward connections (D, from aHP to TP) only. E:

333 Short arrows depict driving input and long arrows depict bilinear modulations.

334 **Fig 5. Results of Bayesian Model Selection (BMS)**

335 BMS was performed on two levels. Family selection of backward, forward and

336 recurrent TP to aHP connectivity (left) and model selection for the backward

337 model-subspace containing 15 models, with all possible combinations of context

338 modulation on aHP to TP connections (middle). The winning model 2 shows

339 effective backward connectivity from left aHP to right TP (right). Exceedance

340 probabilities (EP) are reported as a measure of relative model fit.

341

342 Discussion

343

344

345 In social cognition research, episodic simulation describes the use of prior
346 experiences to infer others' mental states, a process that requires the integration
347 of semantic memory (SM), which represents general knowledge, with
348 autobiographic episodic memory (AEM), which refers to personal events. The
349 present study set out to map the integration of SM with AEM onto the
350 connectivity of two brain regions, which are key for processing of different
351 memory types: the temporal pole (TP), implicated in SM, and the hippocampus
352 (HP), implicated in AEM. Our results indicate for the first time that crossed-
353 hemispheric connectivity from left anterior HP to the right TP is a pillar for
354 episodic simulation. This study not only redefines the role of TP in mnemonic
355 integration, but also points to the lateral specialization of TP, which has
356 remained widely obscure. While the left TP was found to be particularly involved
357 in mental operations related to language processing, the right TP plays a role in
358 the integration of episodic memory. A crossed-hemispheric mechanism for
359 episodic simulation was found in the present study consistently during internally
360 (rest) and externally (task) driven cognition, highlighting the relevance to study
361 brain organization of both functional states in combination.

**362 The right temporal pole integrates episodic with semantic memory during
363 social cognition**

364 Unlike all previous accounts defining TP function, our results indicate that the
365 right TP is particularly involved in the integration of SM with AEM. The semantic
366 hub account, for example, argues that TP is responsible to link perceptual

367 information with semantic memory across modalities [22,23]. Furthermore, TP
368 is prominently implicated in socio-emotional operations like processing of
369 language [47], faces [80] and social concepts [49,81]. In this context, TP was
370 conceptually not only linked to semantic memory, but also to episodic memory.
371 Olson et al. [46] for example suggested that TP mediates between perceptual
372 input and biographical knowledge. In a similar vein, Frith and Frith [55] argued
373 that during mentalizing, TP retrieves social knowledge from autobiographical
374 memory. Despite inconsistencies regarding TP's laterality differences [82], the
375 right TP seems to be particularly involved in emotion processing [46,83].
376 Findings on backward projections from HP to the amygdala during processing of
377 valenced contextual information corroborate links of episodic memory and
378 emotional content [84-86]. We suggest that the right TP is more often reported
379 in the context of emotion processing because of its function to integrate episodic
380 memory, while the left TP might be more engaged when language processing is
381 involved.

382 Indeed, the left TP is usually associated with name retrieval [81,87-89], whereas
383 the right TP is associated with retrieval of episodic knowledge of familiar or
384 famous faces [6,90-93]. The right TP reliably responds to empathy and theory of
385 mind tasks [9,50,82,94], when pairing a fearful sentence with a visual scene [95],
386 processing of social (e.g. 'ambitious' 'honorable') vs. animal concepts (e.g.
387 'trainable' 'healthy') [49,96] and for personally relevant compared to non-
388 personal memories [42], i.e. tasks, which require the integration of AEM's.
389 Furthermore, psychological and socio-emotional problems are particularly
390 pronounced in patients with damage to the right TP [97-100], which might rely
391 on the disability to integrate AEMs. One study has shown reduced hippocampal-

392 temporopolar functional connectivity as a biomarker for diagnoses of social
393 anxiety disorder. This feature disappeared after 8 weeks of treatment with the
394 selective serotonin reuptake inhibitor (SSRI), paroxetine concomitant with a
395 decrease of symptom severity [101].

396 The left TP, however, was found to be involved in verbal processing like
397 learned name retrieval [102] or processing of short narratives [103,104].
398 Evidence for enhanced RSFC to the temporo-sylvian language network for the
399 left compared to the right TP reinforces its specialization for language [105].

400 Our study is the first to link these pieces of evidence of TP function to
401 lateral specialization for mnemonic integration. This is supported by crossed-
402 hemispheric connections of the right TP to the hippocampal episodic memory
403 system.

404 **Hemispheric specialization for different memory types enables episodic**
405 **simulation**

406 Resting state functional connectivity (RSFC) revealed a crossed-hemispheric
407 functional coupling of right TP and left aHP in two independent data sets. ROI
408 analyses have shown significantly stronger functional connectivity of aHP
409 bilaterally to the right TP compared to the left TP (Fig 3), which was supported
410 by weighted lateral indices (LI_{ws}) showing a right-lateralization to the right
411 hemisphere, for TP, and to the left hemisphere for aHP. In line with this, task-
412 based effective connectivity (TBEC) analysis using dynamic causal modeling
413 (DCM) and Bayesian model selection (BMS) revealed that the left aHP exerts
414 backward projections to the right TP as a function of context information and
415 episodic simulation (Fig 5).

416 Neural propagation across hemispheres, between left HP and right TP is
417 most likely conveyed via the anterior commissure [106]. Spherical
418 deconvolution tractography has shown that the main commissural pathway, the
419 corpus callosum, has absence or scarcity of projections to the anterior temporal
420 lobe in humans [106]. Even though the role of the anterior commissure is not
421 well understood to date, it is suggested that it may be specifically responsible for
422 inter-hemispheric transfer for this rostral pathway in the temporal lobe [107].
423 The importance of the anterior commissure as inter-hemispheric cross route
424 was recently supported by a study showing that widespread inter-hemispheric
425 functional connectivity remained intact in rhesus monkeys when sparing the
426 anterior commissure from complete commissurotomy [108].

427 Hemispheric specialization with commissural integration is discussed as
428 evolutionary advantage. In hemispheric specialization actual brain function is
429 retained, but the emergence of higher-order cognitive skills becomes enabled
430 [109]. Language is one example for an advanced cognitive ability, which is highly
431 specialized in the left hemisphere in most humans, and in its complexity unique
432 to the human species [110,111]. Integration across hemispheres is highly
433 important for lateral specialization (e.g. [112]). Hemisphere specific allocation to
434 memory sub-functions could enable humans to successfully engage in episodic
435 simulation and complex social interactions thereby enhancing evolutionary
436 viability.

437
438 **Internal and external processing modes co-operate during social cognition**

439 During rest, participants engage in higher order cognition with self-referential
440 content like thinking about past events or simulating future events, reflecting

441 about social interactions and current concerns, performing goal-directed
442 planning and mental inferences about characteristics of self and others
443 [62,64,66,113,114]. These processes are linked to retrieval of autobiographic
444 memory indicating episodic simulation as one key cognitive operation during
445 rest [115,116].

446 During rest, our results show a crossed-hemispheric coupling of the
447 right TP and left aHP during internally driven episodic simulation, while
448 conclusions on directionality is only possible by TBEC. TBEC using DCM extends
449 evidence from RSFC by showing effective connectivity from left aHP to right TP, a
450 finding that needs replication during rest using stochastic dynamic causal
451 models for example [117,118].

452 An internal processing mode is most prominently associated with the
453 default network (DN) [119,120]. The DN is not only involved in internally driven
454 cognition, but also in tasks that require internal mentation for external task
455 demands like generation of new ideas [121], social working memory [122] and
456 theory of mind [123,124]. In everyday life, internal and external processing
457 modes naturally fluctuate over time [125]. Consistently, intrinsic brain
458 architecture is discussed as a neural baseline activity, a standard state of the
459 brain, which shapes and prepares extrinsic (task-induced) network architectures
460 and replays extrinsic activity during rest [126-131]. In line with this, a strong
461 correspondence between intrinsic and extrinsic network architectures was
462 shown by Cole et al. [132], who compared functional connectivity during rest
463 and multiple tasks (social, emotional, n-back, motor etc.) and revealed striking
464 overlap of network activity irrespective of task. Dixon et al. [133] suggested that
465 a reciprocal interplay of processing modes is mediated by processing demands.

466 Co-occurrence and co-operation between internally and externally oriented
467 modes is possible to the extent that both require a balanced amount of cognitive
468 load with minimal interference [133], a state that likely occurs during social
469 interactions.

470 Real-life social interactions and social cognition tasks might be an
471 excellent case of mutual cooperation of internal and external processing modes.
472 Social interactions demand the combination of external socio-emotional cues like
473 language, facial expressions and biological motion with internal socio-emotional
474 cues like attending to one's own feelings and drawing inferences on others'
475 mental states. The present study shows that crossed-hemispheric connectivity of
476 left aHP and right TP is at the core of episodic simulation in a social context and
477 has equally been observed during rest and during task. For social cognition, we
478 therefore suggest to study internally and externally driven brain organization
479 within a unified framework.

480 **Limitations**

481 The mapping of episodic simulation on the connectivity of two circumscribed
482 brain regions bears strengths and weaknesses. Other brain areas involved in
483 mnemonic integration and episodic simulation are neglected, which is
484 disadvantageous considering the network complexity of the human nervous
485 system. The focus on two brain regions, on the other hand, protects against
486 combinatorial explosion within the DCM framework and enables precise
487 evidence for connectivity on a meso-scale. This generates hypotheses for
488 dynamics within large-scale networks. A putative control function of

489 ventrolateral prefrontal cortex on aHP to TP coupling for example might be of
490 future interest [134].

491 The risk of “reverse inference”, the inference on the engagement of a
492 particular cognitive process from the activation of a particular brain region
493 [135,136] may be another caveat of the present study. Although episodic
494 simulation is strongly supported by the results and by the literature, other
495 experimental designs with systematic variations of AEM and SM should address
496 mnemonic integration during episodic simulation.

497 However, note that patients with Alzheimer’s disease and
498 neurodegenerative changes in medial temporal and anterior temporal regions,
499 show impairment in using episodic memory for the simulation of future events
500 [137], strongly suggesting that activity in HP and TP is critical for episodic
501 simulation.

502 **Conclusion**

503
504 This study shows that the retrieval of self-referential experiences helps
505 individuals to put themselves into the shoes of another person. A novel
506 underlying crossed-hemispheric mechanism was discovered, which is
507 characterized by backward projections from the left anterior hippocampus (aHP)
508 to the right temporal pole (TP). Given that both regions are specialized for
509 different memory types, namely the left aHP for autobiographic episodic
510 memory (AEM) and the right TP for emotional semantic memory (SM), the
511 mechanism points to the importance of mutual co-operation and hemispheric
512 integration for advanced memory-based social cognition. In addition, the study
513 shows state-dependent similarities between functional and effective connectivity

514 suggesting to study resting state and task-based brain organization within a
515 unified framework.

516 By showing the crucial impact of episodic simulation on empathy-
517 capabilities, our findings are important for psychiatric disorders with deficits in
518 emotional reactivity such as autism spectrum disorder. Testing how the present
519 crossed-hemispheric mechanism relies on fiber strength of callosal connections
520 would be of further interest, in particular in patient groups with impaired social
521 functioning.

522

523 **Methods and Materials**

524

525 **Participants and data acquisition.** Twenty-eight right-handed healthy
526 volunteers (mean age 29.85 ± 8.55 (sd), 1.61(se), min = 19, max = 48, years (9
527 males, 19 females)) without history of any neurological or psychiatric disorder
528 participated in the study. Blood oxygen level-dependent (BOLD) fMRI was
529 measured during rest for eight minutes (white fixation cross on black
530 background, eyes open) (Experiment 1) before the beginning of the task
531 (Experiment 2). Both data sets were acquired with a 3T Siemens (Erlangen,
532 Germany) Tim Trio MRI scanner at the Dahlem Institute for Neuroimaging of
533 Emotion (D.I.N.E.) using a 12-channel phased-array headcoil. The same whole-
534 brain T2*-sensitive gradient-echo-planar imaging (EPI) sequence was applied in
535 both experiments [TR 2000 ms; TE 30 ms; voxelsize 3mm³; 240 scans; flipangle
536 70°; FOV 192x192mm; matrix 64x64; 37 slices; 3mm slice thickness; 0.6mm
537 gap]. Before resting state and task data acquisition, a high resolution T1-
538 weighted structural image for registration of the functional data [TR 1900 ms;
539 TE 2.52 ms; flipangle 9°; voxelsize 1mm³; 176 sagittal slices; 1mm slice] was
540 taken. The whole scanning session lasted about 65 minutes. The study was
541 approved by the ethics committee of the German Psychological Society.
542 Participants either received course credit or were paid for their participation.

543 **Resting state functional connectivity (RSFC).**

544 *Seed based functional connectivity analysis.* FMRI data was analyzed using the
545 Statistical Parametric Mapping software package SPM8 (Wellcome Trust Centre
546 for Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk>) implemented in

547 MATLAB (version 2011a; The MathWorks Inc., Natick, MA, USA). The same
548 preprocessing steps were applied to all data sets (see S1 Text for details).

549 A seed-based functional connectivity analysis was conducted with
550 individual time series extracted from a 6mm sphere around TP bilaterally [45 19
551 -36, -50 14 -40; oriented in MNI space]. For definitions of seed coordinates see
552 S1 Text. RSFC analysis was performed using the general linear model (GLM) with
553 a two level approach [138]. On the first level, GLMs were performed containing
554 the high-pass filtered (1/128 Hz) subject-specific signal time courses of gray-
555 matter voxels in a sphere of 6mm radius around the seeds as regressors of
556 interest. Nuisance covariates were added as regressors of no interest including
557 the global signal of three separate brain compartments (all white-matter voxels
558 (WM), all gray-matter voxels (GM), all CSF voxels and all out-of-brain voxels
559 (OOB) as well as 6 head-motion parameters) resulting in a design matrix
560 containing 12 regressors (2 regressors of interest (timecourses of right and left
561 TP) and 10 regressors of no interest (WM, GM, CSF, OOB and 6 movement
562 parameters). To determine spontaneous co-fluctuations of TP bilaterally,
563 individual contrast images corresponding to timecourses of right and left TP
564 regressors were created. All contrast images were taken to the second level
565 (one-sample t tests) for a random-effects (RFX) analysis [138]. The positive
566 functional connectivity is reported at a significance level of $p < 0.05$ family wise
567 error (FWE)-corrected across the whole brain and a cluster extent of 10 voxels.

568 For replication purposes, the same functional connectivity analysis was
569 applied to an independent data set with 198 participants (mean age $21.03 \pm$
570 2.31 (sd), 0.16 (se), min = 18, max = 30, years (45 males, 123 females), details in
571 S1 Text) obtained from the “1000 Functional Connectomes Project”

572 (http://www.nitrc.org/projects/fcon_1000/) [73]. Of this database, we used the
573 set measured in Cambridge and generously provided by Randy L. Buckner. The
574 data set was acquired with a 3T Siemens scanner and a 12-channel vendor
575 headcoil, while the participants had eyes open and saw a fixation cross during
576 rest [TR 3000 ms, 47 slices, voxelsize 3mm³, 119 scans].

577 For both samples, a region of interest (ROI) analysis was applied as
578 additional measure of TP to HP RSFC. The ROIs (HP) were defined as anatomical
579 masks taken from the automatic anatomic labeling atlas [79] as implemented in
580 the WFU Pick Atlas toolbox [71,72]. Parameter estimates were calculated for
581 each subject within a 10mm sphere around individual peaks.

582 For the Berlin sample, individual weighted laterality indices (LI_ws) were
583 calculated for the DN and our main regions of interest, the TP and the aHP using
584 RSFC of bilateral TP. LI's are used as values to quantify relative differences in the
585 engagement of the left versus right hemisphere regions. They provide a
586 mathematical quantification of lateralization and thus are preferable to simple
587 visual inspection. Left hemispheric lateralization was defined as LI_w values > 0.2,
588 and right hemispheric lateralization as LI_w values < 0.2 (as suggested in
589 [74,139,140]). To account for thresholding effects, the LI toolbox was used
590 (version 1.2) [74,75], which generates weighted mean LIs iteratively exploring
591 increasing thresholds using a multithresholded bootstrap-method (see S1 Text).

592

593 **Task based effective connectivity (TBEC).**

594

595 *Dynamic Causal Modeling.* Effective connectivity analysis was performed using
596 DCM10 as implemented in SPM8 (update r5236) to infer effects of mnemonic

597 integration on TP-aHP coupling strengths during social cognition. DCM [141,142]
598 is a Bayesian model comparison procedure used to estimate directed
599 interactions (effective connectivity) between brain regions. DCM models these
600 interactions at the neuronal level and distinguishes between endogenous
601 coupling and context-specific coupling, which are experimentally controlled
602 network perturbations entering the system via driving inputs (for details see S1
603 Text). The present DCM analysis focuses on changes of temporo-hippocampal
604 connectivity by presentation of context information to empathic film clips.

605 *DCM Model Space.* For this purpose, a bilateral 8-area DCM was specified for all
606 subjects with bidirectional endogenous connection between all regions (V1, STG,
607 HP, TP) within and across hemispheres. Primary visual areas (V1 bilaterally)
608 were defined as target regions for visual driving input during all context
609 conditions (Fig 1A.2, 2-3 and 5-6). Auditory cortices (STG bilaterally) were
610 defined as target regions for auditory driving input during all context conditions
611 with music (Fig 1A.2, 5-6; Fig 4A). Figure 4B shows the 15 variants, which
612 include all possible combinations of how the four context conditions
613 (modulatory input) could modulate the connectivity of the four TP-HP
614 connections. To specify the direction of TP-HP coupling, the 15 combinations
615 were modeled in 3 families: a recurrent family (from TP to aHP and aHP to TP,
616 Fig 4B), a forward family (from TP to aHP, Fig 4C) and a backward family (from
617 aHP to TP, Fig 4D). To define a relatively small model space, the direction
618 (forward, backward, recurrent) was assumed to occur equally in both
619 hemispheres and homotopic connections were omitted resulting in 45 models
620 that were fitted and compared for each of the participants.

621 *Timecourse extraction.* Regional time series were extracted on the single-subject

622 level using regions of interest (ROIs) for HP, TP bilaterally. ROIs were
623 constructed using a combination of anatomical and functional criteria (for details
624 see S1 Text and S2 Fig). Each subject's MNI coordinates of the highest t-value
625 within these combined ROIs were surrounded with a sphere of 6mm and used to
626 extract the first eigenvariate based on a t-contrast including all conditions.

627 *Random-Effects Bayesian model selection (BMS)*. Model comparison was
628 implemented using random-effects (RFX) Bayesian model selection to compute
629 exceedance and posterior probabilities at the group level [143]. Exceedance
630 probabilities (EPs) gives the probability of a given model (or family of models)
631 being more likely than any other model (or family of models) in the comparison,
632 given the data. Note that the EP sums to 1 over all models included in the BMS
633 procedure. We also used a hierarchical Bayesian approach [143] to make
634 inferences about model families by performing BMS on 2 levels: First, we
635 compared the forward, backward, and recurrent families of models [144]. Then
636 the models within the winning model family were compared using random-
637 effects BMS. All models were included in the BMS procedure, both when
638 comparing model families and individual models. The posterior distributions of
639 the estimated parameters can then be used to test hypotheses about connection
640 strengths and its modulation quantitatively.

641 *Group statistic of DCM parameters*. For the optimal model, the subject-specific
642 parameter estimates of the modulatory and driving inputs were entered into t
643 tests at the group level using classical random effects analyses; results are
644 reported Bonferroni-corrected in S1 Text.

645

646 **Supporting Information**

647 **S1 Fig. LI analysis.** ROIs covering the DN (top, violet), TP (middle, yellow) and
648 aHP (bottom, green) with weighted LI group means on the right and standard
649 errors of the mean. For LIw-calculations were applied to RSFC patterns of
650 bilateral TP. LI's vary between -1 (right lateralization) and +1 (left
651 lateralization). To note, green and yellow colored ROI's were also part of the DN
652 mask (violet).

653 **S2 Fig. ROIs for DCM timecourse extraction.** TP (yellow), aHP (green), aSTG
654 (red) and V1 (blue).

655 **S1 Table. Positive Resting State Functional Connectivity - Berlin dataset (n
656 = 28).**

657 **S2 Table. Positive Resting State Functional Connectivity - Cambridge
658 dataset (n = 198).**

659 **S3 Table. Parametric BOLD effects of compassion ratings.**

660 **S4 Table. DCM Parameters (B Matrix).** Mean connectivity parameters for the
661 winning model 2 (Fig 5) comprising bilinear modulations of context and music
662 (separated for pos and neg values) on the connection from left aHP to right TP
663 with standard errors (se) in brackets. T tests were performed and t and P values
664 are reported.

665 **S5 Table. DCM Parameters (C Matrix).** Mean connectivity parameters for the
666 winning model 2 (Fig 5) comprising driving input with standard errors (se) in
667 brackets. T-tests were performed and t and P values are reported.

668

669 **S1 Text. Supporting methods and results.**

670

671 **Acknowledgements**

672 The authors thank Mareike Voget for help with data acquisition and Sepideh

673 Sadaghiani for help with data analysis.

674

675 **References**

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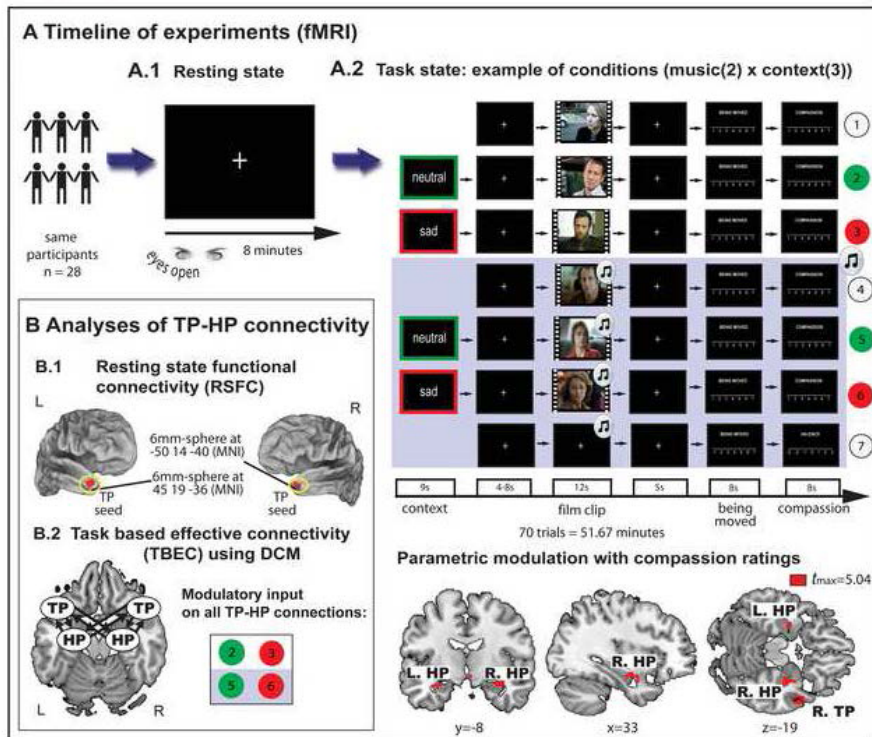
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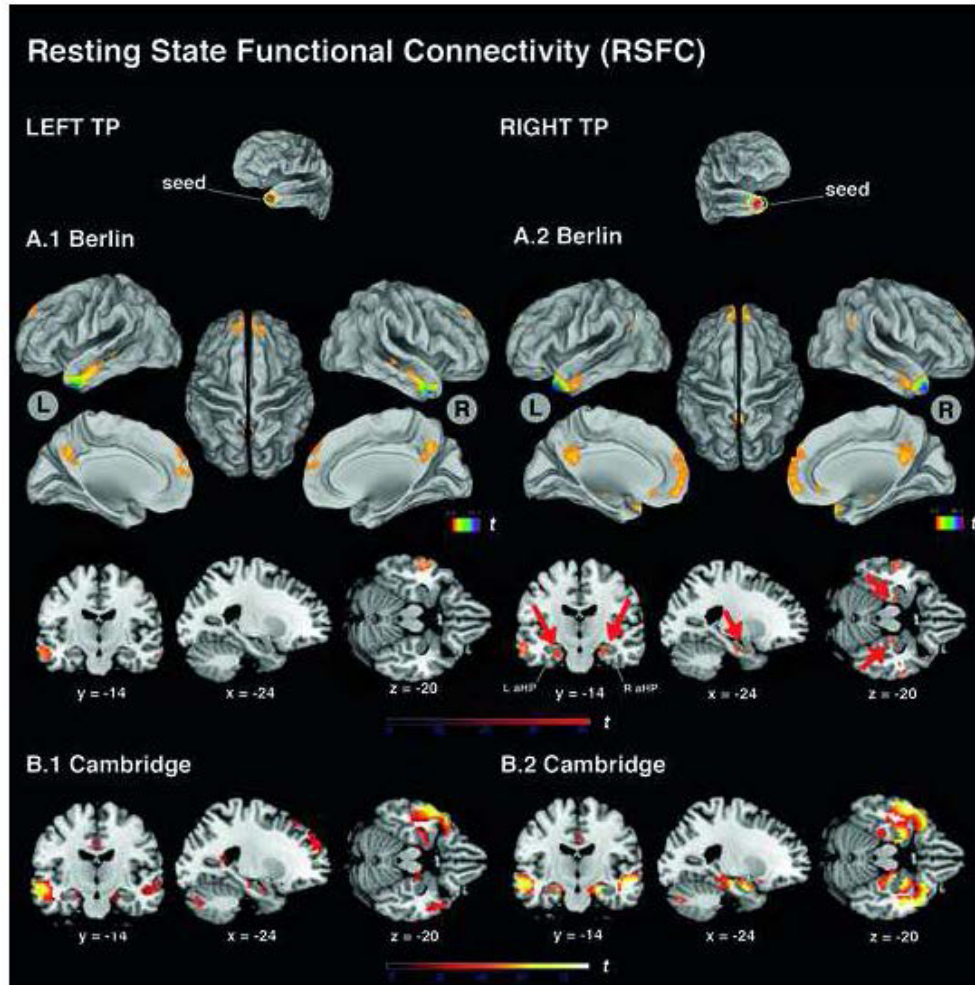
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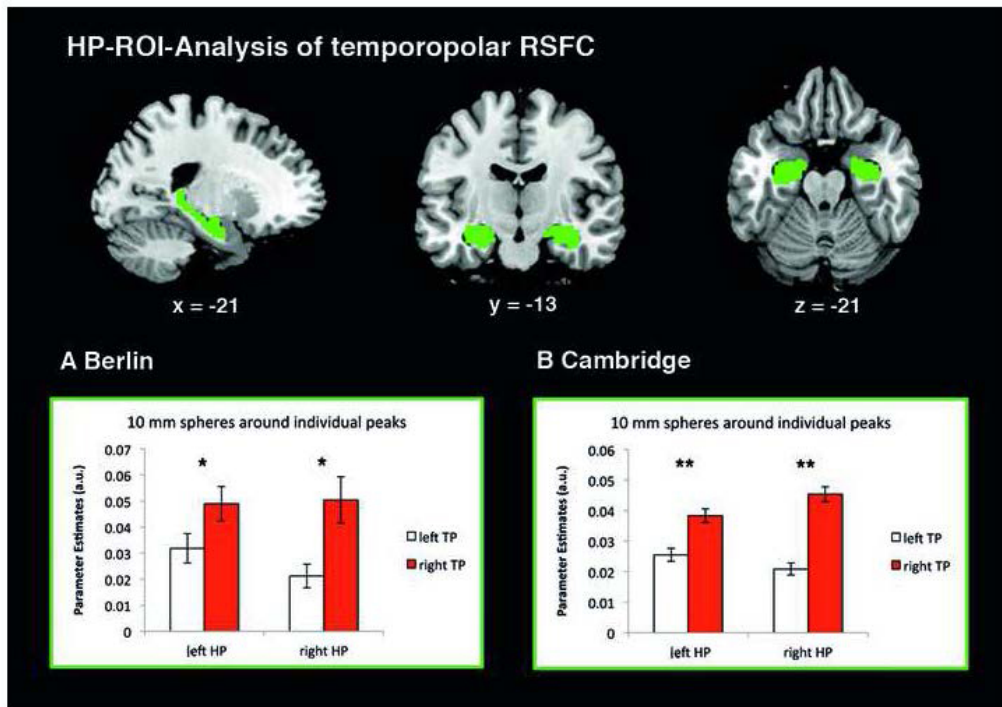
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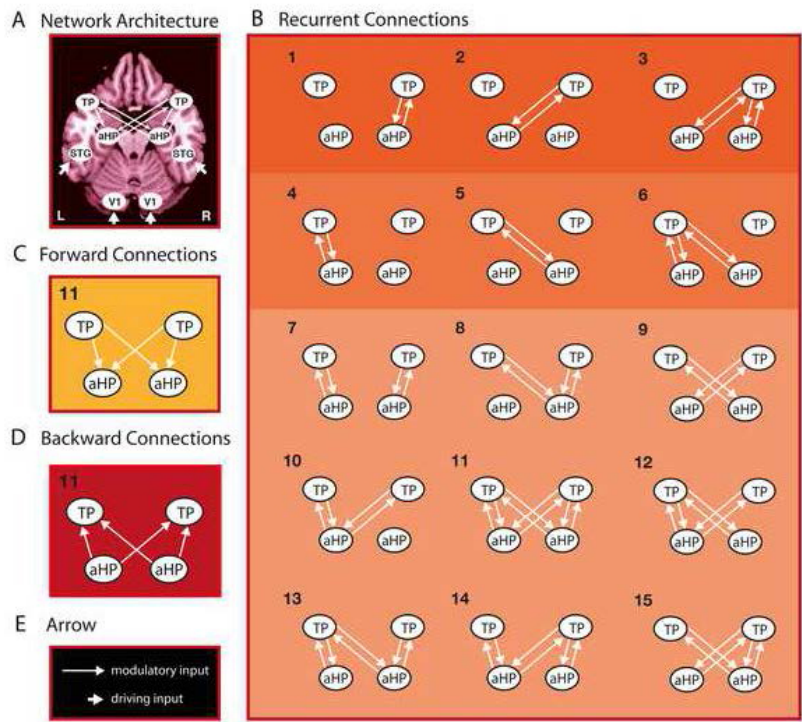
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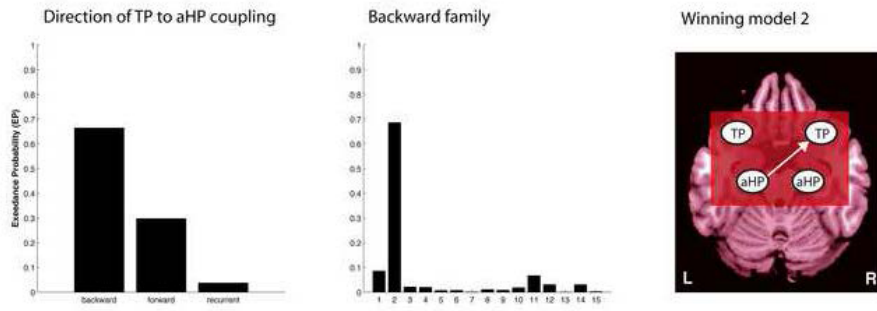
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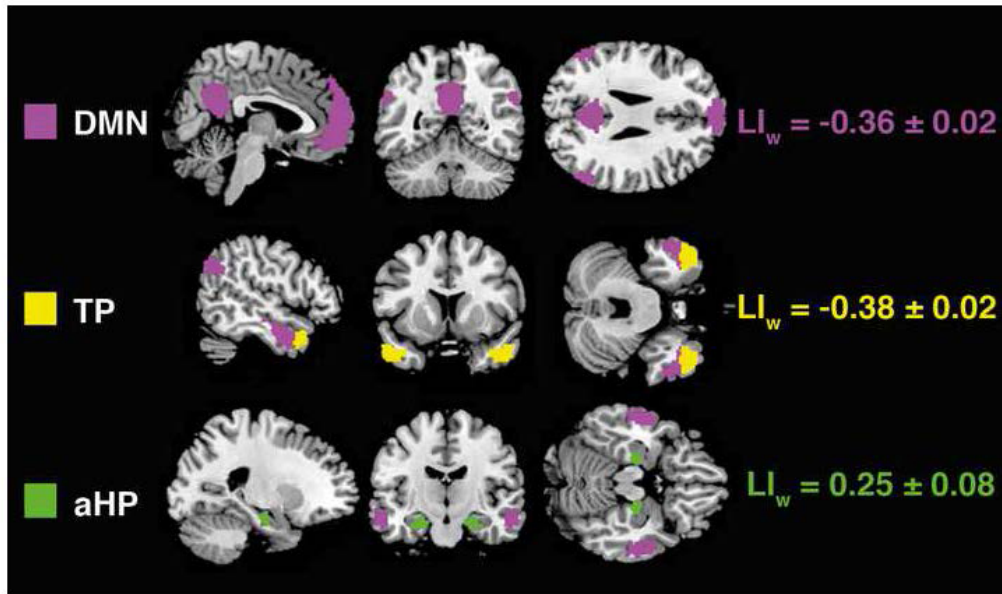
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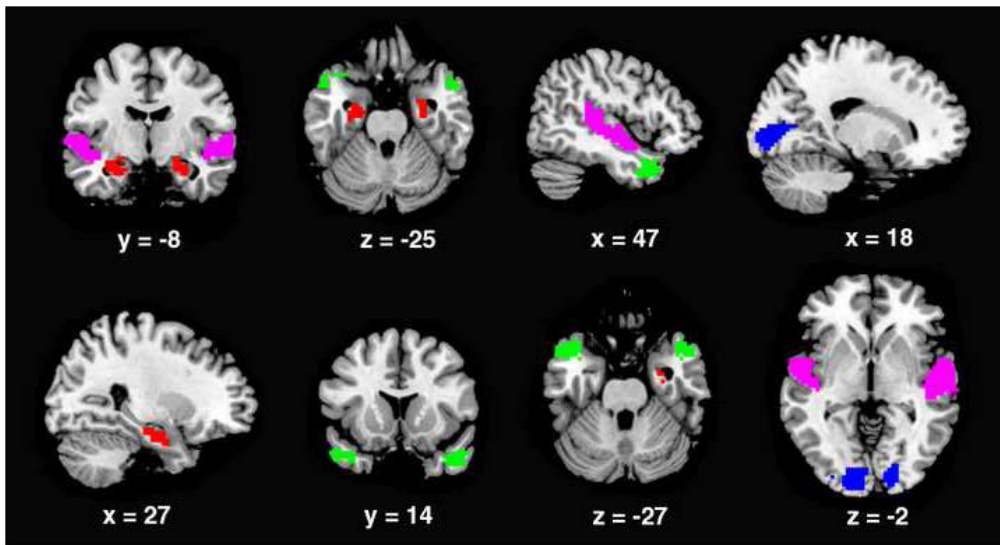
Figure

Figure: S1 Fig.tif



Figure

Figure: S2Fig.tif



Project 4

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<http://dx.doi.org/10.1016/j.plrev.2015.04.025>