Aus der Klinik für Psychiatrie und Psychotherapie
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DISSERTATION

Linking Self-control to Interoceptive Prediction – a Behavioral Study and a Functional Magnetic Resonance Imaging Study

Der Zusammenhang zwischen Selbstkontrolle und interozeptiver Prädiktion – eine Verhaltensstudie und eine funktionelle Magnetresonanztomographie-Studie

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Table of content / Inhaltsverzeichnis

List of Tables

List of Abbreviations

ANOVA	Analysis of variance
CO2	Carbon dioxide
dlPFC	Dorsolateral prefrontal cortex
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
GLM	General Linear Model
O2	Oxygen
preSMA	Pre-supplementary motor area
ROI	Region of interest
TPJ	Temporo-parietal junction
vlPFC	Ventrolateral prefrontal cortex

Abstract

Introduction: Self-control is important for physical and mental health; however, its neuronal mechanisms remain poorly understood. In line with recent theories of interoceptive inference, I hypothesized that successful self-control relies on the ability to anticipate possible outcomes of a self-control decision as future interoceptive states and to subsequently choose the predicted interoceptive decision outcome most consistent with long-term homeostatic goals. To investigate the association of self-control and interoceptive prediction as well as neuronal processes underpinning this relationship, we conducted a behavioral study and a functional magnetic resonance imaging (fMRI) study.

Methods: In our behavioral study, we implemented two tasks in a within-subject design with 51 healthy subjects: An inspiratory breathing restriction task to measure the prediction of aversive interoceptive states and a craving downregulation task to measure self-control. We then explored whether behavioral measures of interoceptive prediction and self-control were correlated. In our second study (n = 39), we replicated the same two tasks in an fMRI-scanner. I first correlated the obtained behavioral measures, and subsequently used univariate analyses to identify peak-voxel brain activations associated with the behavioral measures of self-control and interoceptive prediction.

Results: In our first study, we showed that the level of interoceptive prediction correlated with two independent measures of self-control, i.e., the downregulation of craving for unhealthy snacks and a measure of trait self-control. Thus, individuals with more self-control were more accurate in the prediction of the upcoming breathing restriction or even overestimated it. In our second study, I replicated the previously reported behavioral association of self-control and interoceptive prediction with an independent sample of subjects. Univariate analyses of the fMRI data revealed that activations of the anterior insula and preSMA were associated with both self-control and interoceptive prediction.

Discussion: Both studies demonstrated that self-control is directly associated with interoceptive prediction. I suggest that the anterior insula and preSMA partially account for this relationship as they might be involved in the neuronal processing of self-control decisions related to the prediction of future interoceptive states. Our results are of high relevance for research on psychiatric disorders such as anorexia nervosa or addiction disorders, as these are often characterized by both altered self-control and altered interoceptive processing. As I could show that the anterior insula and preSMA underlie this association, neurofeedback and brain stimulation approaches targeting these areas could be investigated as potential treatment targets.

Zusammenfassung

Hintergrund: Selbstkontrolle stellt einen wichtigen Faktor für körperliche und psychische Gesundheit dar; die neuronalen Mechanismen von Selbstkontrolle sind jedoch bisher nur unzureichend verstanden. In Anlehnung an Theorien der interozeptiven Inferenz untersuchte ich, ob erfolgreiche Selbstkontrolle auf der Fähigkeit beruht, mögliche Ergebnisse einer Selbstkontrollentscheidung als interozeptive (d.h. körperliche) Zustände vorherzusagen. Um den Zusammenhang zwischen Selbstkontrolle und interozeptiver Prädiktion sowie die zugrundeliegenden neuronalen Mechanismen zu erforschen, führten wir eine Verhaltensstudie und eine funktionelle Magnetresonanztomographie (fMRT)-Studie durch.

Methoden: In unserer Verhaltensstudie ließen wir gesunde Proband*innen (n = 51) jeweils zwei Aufgaben durchführen: Eine inspiratorische Atemrestriktionsaufgabe, um die Vorhersage aversiver interozeptiver Zustände zu messen, und eine Selbstkontroll-Aufgabe der Herunterregulierung des Verlangens nach Snacks. Anschließend untersuchten wir, ob Werte der interozeptiven Prädiktion und der Selbstkontrolle miteinander korrelierten. In unserer zweiten Studie (n = 39) replizierten wir die gleichen zwei Aufgaben in einem fMRT-Scanner. Zunächst korrelierte ich die Verhaltenswerte für Selbstkontrolle und interozeptive Prädiktion und verwendete anschließend univariate Analysen, um Gehirnareale zu identifizieren, deren Peak-Voxel-Aktivierungen mit den erhobenen Verhaltenswerten assoziiert waren.

Ergebnisse: In beiden Studien konnten wir mit unabhängigen Proband*innengruppen zeigen, dass interozeptive Prädiktion mit zwei Maßen für Selbstkontrolle korreliert (Erfolg bei der Herunterregulierung des Verlangens nach Snacks, sowie Trait-Selbstkontrolle). Höhere Selbstkontrolle zeigten dabei diejenigen Proband*innen, die die bevorstehende Atemeinschränkung korrekt vorhersagten oder sogar überschätzten. Analysen der fMRT-Daten in Studie 2 zeigten, dass die Aktivität der anterioren Insula und des prä-supplementär-motorischen Areals (präSMA) sowohl mit Selbstkontrolle als auch mit interozeptiver Vorhersage korrelierte.

Diskussion: Die Ergebnisse beider Studien weisen darauf hin, dass Selbstkontrolle mit interozeptiver Prädiktion assoziiert ist. Womöglich sind dabei unter anderem die anteriore Insula und das präSMA für die neuronale Verarbeitung von Selbstkontrollentscheidungen im Zusammenhang mit der Vorhersage zukünftiger interozeptiver Zustände verantwortlich. Unsere Ergebnisse sind von hoher Relevanz für die Erforschung psychischer Erkrankungen wie Anorexia nervosa oder Suchterkrankungen, da diese häufig sowohl durch veränderte Selbstkontrolle als auch durch veränderte interozeptive Verarbeitung gekennzeichnet sind. Da

ich zeigen konnten, dass die anteriore Insula und das präSMA der Assoziation von Selbstkontrolle und interozeptiver Prädiktion zugrunde liegen, könnten Neurofeedback- und Hirnstimulationsansätze, die auf diese Areale abzielen, als mögliche Therapien erforscht werden.

1. Introduction

1.1. Self-control

The human capacity for self-control has been an important factor in humans' cultural development and success. This is evidenced by findings of about 500,000-year-old tools which required a high degree of distress tolerance, forward planning, and time and energy investment for their production (1). The increased capacity for self-control probably served as a key selection advantage, as it not only enabled more efficient resource exploitation, but also constituted a prerequisite for social collaborative practices such as hunting or food sharing.

In many aspects of our lives, we rely on self-control, defined as the ability to subdue immediate temptations, or tolerate short-term costs when pursuing long-term goals (2–4). High self-control contributes to desirable outcomes such as physical health and psychological well-being, successful social relationships, academic and professional achievement, and ethical decision-making (5,6). The importance of self-control is particularly evident when it fails and individuals act against their intentions, such as in addiction disorders. Investigating self-control mechanisms is therefore of great scientific relevance.

Yet, there are highly conflicting models that attempt to explain our brain's unique capacity for self-control. The dual-system model, on the one hand, assumes that self-control results from the competition between a "hot" impulsive system - located in limbic brain areas and the ventromedial prefrontal cortex - and a "cold" cognitive control system in the dorsolateral prefrontal cortex (7). To achieve long-term goals, the slow cognitive system must suppress the impulsive system that seeks immediate rewards. If, for example, someone on a diet is faced with the decision of whether to eat a salad or French fries for dinner, the dual-system hypothesis would suggest that the immediate hedonic urge for French fries must be effortfully inhibited to attain the long-term weight loss goal.

Critics of the dual-system model, however, argue that self-control might often feel like a battle between "hot" impulsive processes and "cold" deliberate ones, but the duality of the subjective impression when exercising self-control may not be reflected as such by underlying neuronal processes (8). Coming back to the person who must decide between eating French fries or a salad, there exists a multitude of other pathways to self-control success apart from processes involving effortful inhibition (9). For instance, the person might consider the approval received from meeting societal beauty standards, could anticipate the sensation of feeling at ease with their body, or focus on the satisfaction of getting closer towards a cherished goal. Dual-system models cannot account for this diversity of self-control behavior by reducing it to an inhibition

process. Instead, critics argue that self-control could be more comprehensively investigated if it were considered a value-based choice (8). Value-based decision-making implies weighing two comparable decision outcomes against each other, rather than as a competition between two opposing systems as assumed by the dual-system hypothesis.

In defining self-control as a special case of value-based choice, the question inevitably arises on what basis values are ascribed to different decision options. A growing body of literature on general decision-making points to the decisive role of homeostatic processes in value-based choices (10–12). It is argued, that the fundamental goal of our brain is to ensure our survival and, to this end, maintain our body within a state of dynamic stability – even though our body is in exchange with an inherently uncertain environment (13). Consequently, self-control choices strive to maintain homeostasis by assigning a higher value to long-term homeostatic goals than to short-term temptations.

However, so far it remains unclear, how our brain represents possible outcomes of a self-control decision and how it compares them to long-term homeostatic goals (4). To further elucidate the relationship between self-control and homeostatic processing, we combined research on self-control with recent theories of interoceptive prediction.

1.2. Interoceptive prediction

Our brain does not have direct access to the truth about the internal body state or the external environment, but relies on noisy and ambiguous sensory data it receives via exteroception (sensory information from outside the body, e.g., sight, olfaction, touch), proprioception (sensory information reflecting the relative spatial position of body parts) and interoception (sensory information from within the body, e.g. autonomic, hormonal, immunological signals) (14). Following the well-established cybernetic principle that any good regulator of a system maintains an internal model of that system (15), our brain constantly computes a predicted model of the body state based on interoceptive information which is integrated with proprioceptive and exteroceptive data (16). The interoceptive predictive model enables the brain to not only respond to homeostatic deviations but to anticipate physiological needs via Bayesian inference on the basis of prior experiences and incoming interoceptive data (13,14). This process of achieving homeostatic stability by anticipating bodily needs and preparing for their satisfaction even before these needs occur has also been defined by the term “allostasis” (17).

Interoceptive predictive processing is organized hierarchically: Higher levels of the neuronal hierarchy generate top-down predictions of the body states they believe they should occupy to

maintain homeostasis. At every level of the neuronal hierarchy, these descending predictions are compared to bottom-up sensory information (16). If predictions match sensory data, it can be assumed that the predictions must have been generated by an internal model concordant with the actual body state. However, if a top-down prediction does not match the incoming sensory data, a prediction error may arise (14). Following the free energy principle (13), our brain endeavors to minimize prediction errors in order to avoid surprising events as they might counteract homeostasis.

Prediction errors are minimized by two processes that run simultaneously and permanently (13). Perceptual inference, on the one hand, implies updating of the predictive model based on incoming sensory signals. Active inference, on the other hand, does not aim at changing the predicted model, but rather at changing the sensory data so that it becomes congruent to the predicted model. In doing so, our brain either filters incoming sensory signals selectively or performs actions that confirm the interoceptive prediction. This includes autonomic regulation as well as influences on decision-making in the service of allostasis (18). For example, in hypoglycemia (sensed through interoception), active inference on a low level would lead, i.a., to glucagon-mediated gluconeogenesis in the liver and a consecutive increase in blood glucose levels. Active interoceptive inference on a higher cortical level would imply the preparation of adaptive allostatic behavior, such as the preparation and consumption of a meal.

Active inference requires the prediction of how an action, e.g., eating, will change sensory signals, e.g., blood glucose levels. Before taking a decision, the brain thus predicts all possible decision outcomes across multiple timescales (12,19) and then decides for the predicted interoceptive state that shows the least divergence from the preferred (homeostatic) state of the individual (13). Here, again, the brain computes a prediction error, but not a *state* prediction error between incoming interoceptive information and the internal model of the body of that moment, but a *preference* prediction error computed between predicted future action outcomes and the preferred long-term homeostatic model (20). The brain seeks to minimize both *state* prediction errors and *preference* prediction errors based on the assumption that minimizing "surprise", i.e., free energy, is necessary in order to remain within the narrow range of body states compatible with survival (13).

1.3. Study 1: Linking self-control to interoceptive prediction

A large number of studies has shown that decision-making is influenced by both the current body state (21–23) and individuals' interoceptive sensitivity (24–26). Yet, the theory of interoceptive inference goes beyond this claiming that decision-making is based not only on

interoceptive signals reflecting the current body state but also on interoceptive predictions of future body states (16,27). To our knowledge, however, no empirical study had yet examined the extent to which individuals' interoceptive prediction ability is related to decision-making – and to self-control decisions in particular. In two studies (3,4), I addressed the hypothesis that successful self-control depends on the ability to anticipate possible outcomes of a decision as predicted interoceptive states, compare these predictions to long-term homeostatic goals and finally choose the option with the lowest prediction error computed between the predicted interoceptive decision outcome and the internal homeostatic model. For example, when faced with the decision of whether or not to eat a chocolate bar after a nutritious dinner, the brain would predict the possible decision outcomes as future interoceptive states (hyperglycemic vs. normoglycemic body state), compare them to the long-term homeostatic model, and choose the predicted interoceptive state most consistent with long-term homeostatic goals – in this case, probably not eating the chocolate bar. Hence, self-control could be understood as active inference aiming to decrease the interoceptive prediction error to achieve a concordance of the body state with the internal homeostatic model (3). Failures of self-control may in turn be promoted by inaccurate predictions of future body states associated with decision outcomes resulting in behavior that conflicts with long-term homeostatic goals.

In our behavioral study (3) we set up two experiments in a within-subject design to investigate the relationship between interoceptive prediction and self-control. First, an inspiratory breathing restriction task was implemented to measure participants' prediction of an impending aversive interoceptive state. Secondly, participants completed a craving regulation task to measure their self-control success in downregulating the desire for unhealthy snacks using negative future thinking strategies (e.g., "I will gain weight"). Furthermore, participants filled out a self-report questionnaire on trait self-regulation. We hypothesized that the accuracy of interoceptive predictions as measured in the breathing restriction task would correlate with both the degree of self-control success in the craving regulation task as well as with higher scores on a trait measure of self-control. In this first study (3), I was mainly involved in the interpretation of the results and the writing of the paper.

1.4. Study 2: Neuronal substrates underlying the relationship between interoceptive prediction and self-control

In the main study of my dissertation (4), I sought to replicate the experimental set-up of study 1 in an fMRI-environment to investigate the neuronal mechanisms underpinning the relationship between self-control and interoceptive prediction. Since its first description in the early 90s (28,29), fMRI has been extensively used in basic and applied neuroscientific research.

It is considered by many to be “the currently best tool (..) for gaining insight into the brain function” (30) – although it can only indirectly reflect brain activation. fMRI is based on evidence that neuronal activity and a subsequent increased metabolic demand lead to a disproportionate increase in cerebral blood flow, which in turn results in an increased concentration of oxygenated hemoglobin and a lower concentration of deoxygenated hemoglobin in red blood cells (31). Given that the paramagnetic deoxyhemoglobin significantly attenuates the magnetic resonance signal, it can be assumed that the blood oxygenation level dependent (BOLD) response measured in fMRI-studies corresponds to a reduced concentration of deoxyhemoglobin and thus an increased synaptic activity in corresponding brain areas.

I expected that fMRI analyses in study 2 would primarily reveal the engagement of the anterior insula in both the breathing restriction and the craving regulation task (4). The insular cortex, folded deep within the lateral sulcus, is considered as the primary interoceptive brain region (32). It exhibits a posterior-to-anterior gradient: Interoceptive information culminates first in the granular posterior insula and is then passed to the agranular anterior insula (33,34). Based on this primary interoceptive information, the anterior insula integrates cognitive-affective conditions as well as memory information deriving from other brain regions (14) and, finally, is claimed to hold the predicted internal model of the body state (32).

Activation of the anterior insular cortex has been shown in several tasks involving interoceptive processing (for a review see Craig 2009 (34)) but has also been described in the context of intuitive decision-making (25), dietary self-control (35) and emotional and behavioral control (36). Moreover, insular activation has been demonstrated during risky decision-making, suggesting that the anterior insula may be involved in representing future interoceptive states related to the experience of risk (37). Involvement of the anterior insula has also been shown in tasks involving the anticipation of gains and losses (38) as well as the anticipation of pleasant and aversive stimuli (39,40). In light of these previous studies, I hypothesized that the anterior insula is responsible for anticipating future interoceptive states, which I in turn consider to be the basis for successful self-control – and that the anterior insula would therefore be involved in both the breathing restriction and the craving regulation task (4).

As pointed out in study 2 (4), recent evidence suggests that the ventral and dorsal anterior insula are differently involved in interoceptive, emotional and cognitive processing (41–43). While the ventral anterior insula encodes subjective feeling states, the dorsal anterior insula is rather activated in cognitive control tasks and might account for creating and updating motivational states regarding specific actions (44). To this end, I investigated the activation of left and right,

as well as dorsal and ventral anterior insula separately. Apart from the activation of different parts of the anterior insula I expected the involvement of regions that have previously been activated in tasks involving interoceptive processing (i.e., anterior and mid-cingulate cortex) (45,46), or respectively self-control (i.e., TPJ, preSMA, vlPFC and dlPFC) (35,36).

As described in study 2 (4), our analysis scheme involved three different approaches: First, I aimed to replicate study 1 (3) with an independent sample of healthy participants by computing the behavioral association of interoceptive prediction and two measures of self-control, i.e., downregulation of craving, and a trait measure of self-control. Secondly, I used univariate analyses to investigate which brain regions underpin the relationship between interoceptive prediction and self-control. I hypothesized that behavioral measures of self-control and interoceptive prediction would be associated with activations of the anterior insula as well as other regions of interoceptive prediction (anterior and mid-cingulate cortex) respectively self-control (e.g., preSMA, TPJ) during the tasks (within-task-analyses). Furthermore, I hypothesized that brain activations during the breathing restriction task would also correlate with behavioral self-control success in the craving regulation task and, vice versa, that neuronal activations during the craving regulation task would be associated with behavioral measures of interoceptive prediction from the breathing restriction task (between-task-analyses). These between-task relationships would underline the relevance of cortical regions as shared substrates accounting for the relationship between self-control and interoceptive prediction (4). While I conducted analyses of behavioral and respiratory data as well as univariate analyses of the fMRI data in study 2, the publication's second lead author Henrik Walter and colleagues were responsible for an independent third analysis approach, namely a data-driven network-based connectivity analysis of the fMRI data. They hypothesized that behavioral measures of interoceptive prediction and self-control would be associated with the connectivity of neuronal networks, including the anterior insula and areas involved in self-control and interoceptive processing (4).

2. Methods

2.1. Participants

In study 1 (3), 66 healthy, non-smoking young adults from the local population participated. Prior to all analyses, we had to exclude 15 subjects because they either showed no variation in their rating behavior or had higher craving ratings in the self-control condition than in the control condition and thus presumably misunderstood task instructions. The final sample of study 1 included 51 adults free from respiratory diseases and psychiatric disorders (27 women, mean age: 27.51 years). For study 2 (4), I recruited 49 healthy, non-smoking adults, free from

respiratory diseases, psychiatric disorders and common exclusion criteria for fMRI studies (pregnancy, metal implants, unremovable piercings, tattoos and permanent makeup). Prior to all analyses, I excluded 9 individuals because they either showed no variation in their rating behavior, exhibited higher ratings in the self-control condition than in the control condition, or were detected as outliers in the breathing restriction task using the interquartile range approach (47). Furthermore, I excluded one subject due to elevated head movement (mean framewise displacement >0.5mm in one run) resulting in the final sample of 39 (18 women, mean age: 27.22 years). Both our studies were approved by the ethics committee of *Technische Universität Dresden* and participants provided written informed consent in compliance with the Declaration of Helsinki.

2.2. General Procedure

In both studies (3,4), we asked participants not to eat for two hours before coming to the lab. All subjects participated in an inspiratory breathing restriction task and a craving regulation task. The order of the experiments was counterbalanced between participants. After completing both experiments, participants filled out two self-report questionnaires: the *Self-Regulation Scale* (48) and the *Physical Activity, Exercise and Sport Questionnaire* (49).

In study 1 (3), we acquired only behavioral data. Experiments in study 2 (4) took place in a 3T MRI scanner, equipped with a 32-channel head coil. Functional imaging was conducted using a T2*-sensitive one-shot gradient-echo planar imaging sequence (voxel size 2.5x2.5x2.5mm, echo time 25ms, repetition time 2490ms, flip angle 82°). Additionally, we acquired a structural image for spatial reference, using a high-resolution T1-weighted sequence. In study 2, I served as one of the two experimenters during all fMRI appointments, instructed participants and operated the scanner as a certified “advanced user”.

2.3. Breathing restriction task

To measure participants’ interoceptive prediction of an aversive body state, we needed to find a well-validated set-up that would (a) induce a strong aversive body state that would not easily habituate, (b) be fMRI-compatible and (c) not significantly change CO2-levels. Altered arterial CO2 concentrations affect the cerebral blood flow (50) and can, thus, result in misleading signal-activation in fMRI imaging. We chose to implement inspiratory breathing loads which have been demonstrated to serve as a powerful tool to measure participants’ predictions about impending aversive body states on both a sensory and affective dimension (51). They are air-flow-dependent loads that induce strong subjective feelings of dyspnea without changing CO2 and O2 levels (52).

Throughout the breathing restriction task, subjects were required to breathe through an oronasal mask attached to a T-shaped connector with one inspiratory and expiratory check valve each, separating the inspiratory and expiratory airflow. A three-meter-long plastic tube was connected to the inspiratory check valve. The examiner could then insert a linear resistor into the end of the tube establishing a constant resistance to inspiratory airflow of 40cmH20/liters per second. In study 2 (4), I monitored and recorded CO2 and O2-volumes in inspiratory and expiratory air to ensure constant levels throughout the experimental session. Additionally, I recorded airflow, breathing frequency and inspiratory time.

Prior to the experiments, we asked participants to breathe through the mask with and without breathing restriction and rate their experience with and without restriction along three dimensions (dyspnea, pleasantness, unpleasantness) to establish a baseline. Collecting baseline ratings allowed us to evaluate if the breathing restriction successfully induced dyspnea and negative emotional experience. Moreover, we included baseline ratings as covariates in the behavioral correlation analyses, since we were mainly interested in the difference scores between anticipated and experienced breathing restriction (i.e., prediction errors), but not in the extent of dyspnea or negative emotion caused by the breathing restriction.

During the experimental session itself (which in study 2 took place in an fMRI scanner), participants completed a simple continuous performance task to ensure their attention to the screen. The changing of the background color of the screen from black to yellow served as a cue that a breathing restriction of a duration of 40 seconds would follow in one third of the cases. The probabilistic design of the experiment allowed us to maximize the number of anticipation trials (i.e., trials during which participants saw the yellow screen) while minimizing the total duration of the experiment (3,4). After each breathing restriction, participants rated how they felt with the breathing restriction; if the breathing restriction did not occur after the anticipation period, they were asked how they would have felt with the breathing restriction. Participants rated both the experienced and anticipated breathing restriction on a 5-point Likert scale along three dimensions: level of dyspnea (sensory dimension), unpleasantness and pleasantness (affective dimension).

As behavioral measures of participants' interoceptive prediction, we calculated the difference scores between ratings of the experienced body state during the breathing restriction and ratings of the anticipated body state separately for each of the three scales. Thus, we obtained three values for each participant: Δ-dyspnea, Δ-unpleasantness, and Δ-pleasantness. Positive values of Δ-dyspnea signified that participants underestimated the breathing restriction (positive

prediction error), whereas negative values indicated an overestimation of the upcoming body state (negative prediction error). To assess overall task effects, we conducted two repeated-measure ANOVAs and post-hoc paired sample t-tests separately for baseline measures and behavioral measures obtained in the experimental session.

For quality control of the recorded respiratory measures in study 2 (4), I calculated means of the obtained measures (inspiratory time, breathing frequency, airflow, volume of CO2 expired) for the three conditions *baseline*, *anticipation* and *breathing restriction* and compared them using two-sample t-tests on a group-wise level.

In study 2, I conducted all analyses of behavioral and respiratory data.

2.4. Craving regulation task

In addition to the breathing restriction task, all participants completed a cognitive emotion regulation task suitable to measure self-control success. Participants saw pictures of tasty but unhealthy snacks and were asked to either anticipate the sensation of indulging (control condition) or downregulate their craving (self-control condition) using negative thoughts about future consequences of indulging (e.g., "If I eat a lot of these unhealthy snacks, I will gain weight"). The self-control condition and the control condition were each encoded by visual cues presented shortly before pictures of the snacks. After each trial, participants rated the extent of their craving for the snack (sensory dimension) and the unpleasantness and pleasantness they felt (affective dimension) on a 5-point Likert scale.

Similar to the breathing restriction task, we computed the behavioral measures of interest as the difference scores between respective ratings of the self-control and control condition along the three scales (Δ-craving, Δ-unpleasantness, Δ-pleasantness). Thus, higher values of Δ-craving indicated more self-control success. To evaluate overall effects of the self-control task, we computed a repeated-measure ANOVA and subsequent paired sample t-tests between behavioral measures of the self-control and control condition along the three scales. In study 2, I conducted these analyses.

2.5. Behavioral analyses across tasks

In both studies (3,4), we first explored whether behavioral measures of interoceptive prediction (breathing restriction task) and self-control (craving regulation task) would correlate. To this end, we conducted three partial correlation analyses, along the sensory dimension (i.e., between Δ-craving and Δ-dyspnea), and along the affective dimension (i.e., between values of "Δ-unpleasantness" and "Δ-pleasantness" of the respective tasks). We included breathing baseline

measures, age, and physical exercise scores (obtained through the *Physical Activity, Exercise and Sport Questionnaire* (49)) as covariates. Secondly, we correlated behavioral measures of the craving downregulation task (e.g., Δ-craving) with the absolute difference scores obtained in the breathing restriction task (e.g., |Δ|-dyspnea). While directed difference scores (i.e., Δ) distinguish between over- and underestimation, absolute difference scores (i.e., |Δ|) serve as measures of "interoceptive prediction accuracy" (3,4). Thirdly, we conducted a partial correlation analysis between scores of the *Self-Regulation Scale* (48) and Δ-dyspnea and included the same covariates reported above. Finally, to establish that the association between self-control and interoceptive prediction depends solely on the difference scores (i.e., prediction errors), we computed all previous correlations with the absolute rating values of dyspnea and craving. In study 2, I performed all of these analyses.

In study 1 (3), we applied two-sided testing for all correlational analyses. In study 2 (4), I applied one-sided testing for those correlational analyses where I had a priori knowledge about the direction of effects due to the first study (i.e., correlation between Δ-dyspnea and Δ-craving, and between Δ-dyspnea and *Self-Regulation Scale*). For all other correlational analyses, I used two-sided tests.

2.6. fMRI analyses

2.6.1. Regions of interest for statistical analyses

To reduce multiple comparisons, I limited univariate analyses of the fMRI data of study 2 (4) to a set of a priori defined regions of interest (ROIs) based on a systematic review of the literature on interoceptive processing and self-control. I selected the anterior insula as the main ROI for both experiments given its pivotal role in interoceptive processing and self-control (34–36). Since recent evidence suggests that left and right, as well as dorsal and ventral insula are differently involved in interoceptive, emotional and cognitive processing (42–44), I specified 4 separate ROIs for the anterior insula. For the breathing restriction task, I additionally defined the anterior and mid-cingulate cortex as ROIs given that many studies have demonstrated their involvement in interoceptive processing (45,46). For the craving regulation task, I considered the TPJ, preSMA, vlPFC and dlPFC as additional ROIs based on two meta-analyses that point to their implication in dietary self-control (35) and cognitive behavioral and emotional control (36). I created ROIs for standard univariate analyses using the Brainnetome Atlas (53) by combing several small segments across hemispheres. For insula subregions, I did not modify the pre-existing masks.

2.6.2. Preprocessing

To prepare the fMRI data for statistical analyses, I applied a number of preprocessing steps using FMRIPREP (54). Preprocessing included, among others, correction for participants' movements during the scanning session (i.e., motion correction), removal of non-brain tissues such as eyes, skull and cavities (i.e., brain extraction) and spatial transformation of participants' anatomically different images to a standard template (i.e., spatial normalization) (for more detail see publication of study 2, (4)).

2.6.3. Brain-behavior relationship within tasks I: Breathing restriction task

Separately for the two experiments and each subject, I first constructed a general linear model (GLM) using the preprocessed data. The GLM of the breathing restriction task included our three event-related regressors of interest (*baseline, anticipation, breathing restriction*) as well as several covariate regressors (six motion regressors, time points of button-press for the continuous performance task, airflow and volume of CO2 expired). For the contrast of interest, *anticipation* > *baseline*, I then conducted ROI-based and whole-brain one-sample t-tests. The construction of the GLM and the subsequent one-sample t-tests allowed me to evaluate which voxels showed more activation during the anticipation of the breathing restriction than during the baseline condition. However, because in univariate analyses this comparison is calculated separately for each voxel (whole brain or within ROIs) and thus the probability of false-positives would be tremendously high, it is imperative to control for family-wise error (FWE) rates (55,56). In a second step, I additionally applied false discovery rate (FDR) correction (57) to correct for false-positives due to multiple testing across 6 ROIs. Subsequently, I extracted the peak-voxel activations of regions that survived FWE- and FDR-correction and correlated these peak-voxel activations with the obtained behavioral measures (Δ-dyspnea, Δ-unpleasantness, Δ-pleasantness). Again, I applied FDR correction to these results to correct for multiple comparisons.

Additionally, I computed the slope of activation for significant ROIs of the anterior insula, assuming that not only the mean signal reflected by the peak-voxel activation but also the time course of insular activation would contain relevant information about neuronal processes within the anterior insula (4,58). For this purpose, I extracted average time-series across all voxels of the respective insula partition and corrected them for confound signals (6 movement parameters, 2 respiratory measures). I then calculated the slope of signal increase between the time point of maximum and the time point of minimum signal intensity. To obtain the final measure, I computed the mean slope of signal increase across all anticipation trials and subsequently correlated this measure with the three behavioral measures of the breathing

restriction task. For both computational approaches to brain-behavior relationship (i.e., peak voxel activation and insula slope), I included subjects' breathing baseline measures, physical exercise scores and age as covariates.

2.6.4. Brain-behavior relationship within tasks II: Craving regulation task

Similar to the fMRI analyses of the breathing restriction task, I computed a GLM for the craving regulation task with the self-control condition and the control condition as regressors of interest. The six motion regressors were included as covariate regressors. I then conducted ROI-based and whole-brain one-sample t-tests for the contrast of interest, *self-control > control condition*. As in the breathing restriction task, I extracted the peak-voxel activation of those regions that showed significant activation (FWE-corrected p-value <.05, additionally FDR correction for multiple testing across 11 ROIs (57)) and subsequently correlated these with the behavioral measures of the craving regulation task (Δ-craving, Δ-unpleasantness, Δ-pleasantness).

2.6.5. Brain-behavior relationship between tasks

Furthermore, I investigated whether task-specific neuronal activations in one task would be associated with behavioral measures of the respective other task, indicating the existence of shared cortical structures underpinning the association of self-control and interoceptive processing (4). Similar to the within-task brain-behavior analyses, I correlated significant peak-voxel activations and slopes of signal increase from one experiment with the behavioral data obtained in the respective other task. Thereby, I set out to investigate, on the one hand, whether brain activation during the anticipation of the breathing restriction would be associated with the level of self-control success in the craving regulation task and, vice versa, whether the level of brain activation during the downregulation of craving would be related to behavioral measures of interoceptive prediction in the breathing restriction task. I included breathing baseline measures, the physical exercise score and age as covariates.

2.6.6. Functional connectivity analyses

While I conducted the univariate analyses described above, Walter and colleagues applied a network-based task-related functional connectivity approach (59,60) to identify networks whose connectivity during the experiments would be linked to the obtained behavioral measures both within-tasks and between-tasks (see publication of study 2 for more details (4)).

3. Results

3.1. Behavioral analyses

In both studies (3,4), we first assessed overall task effects of the breathing restriction and the craving regulation task. The evaluation of the baseline ratings of the breathing restriction task revealed that the inspiratory breathing restriction induced significantly higher levels of dyspnea and unpleasantness as well as lower levels of pleasantness (significant interaction effects with $F(2, 36.47, p<.001)$ in study 1 and $F(1.64,62.33, p<.001)$ in study 2, for mean values see table 1). Our results confirm that the implemented breathing restriction paradigm is a successful tool to induce strong aversive interoceptive states.

Table 1: *Results of baseline ratings of the breathing restriction task in study 1 (3) and study 2 (4): mean values and significance as assessed with paired sample t-tests between baseline ratings with and without breathing restriction.*

		Without breathing restriction	**With breathing restriction**	**Significance**
Dyspnea	*Study 1:*	1.56	2.72	p<.001
	Study 2:	1.76	3.03	p<.001
Pleasantness	*Study 1:*	2.84	2.12	p<.001
	Study 2:	3.0	1.94	p<.001
Unpleasantness	*Study 1:*	2.70	3.61	p<.001
	Study 2:	2.47	3.49	p<.001

During the experimental session of the breathing restriction task, we observed a significant difference between ratings of *anticipated breathing restriction* and *experienced breathing restriction* along the three scales (study 1: $F(2, 32.01, p<.001)$; study 2: $F(1.44, 54.81, p<.001)$). Participants anticipated the breathing restriction to be more pleasant and less unpleasant than actually experienced. While participants in study 1 anticipated less dyspnea than experienced, the anticipated and experienced levels of dyspnea in study 2 did not differ significantly (see table 2).

Table 2: *Overall task-effects in the breathing restriction task in study 1 (3) and study 2 (4): mean values and significance as assessed with paired sample t-tests between ratings of anticipated vs. experienced breathing restriction.*

		Anticipated breathing restriction	Experienced breathing restriction	Significance
Dyspnea	*Study 1:*	2.19	2.66	p<.001
	Study 2:	2.48	2.55	p>.05
Pleasantness	*Study 1:*	2.77	2.44	p<.001
	Study 2:	2.5	2.35	p<.01
Unpleasantness	*Study 1:*	2.61	3.19	p<.001
	Study 2:	2.62	2.82	p<.01

In both studies (3,4), participants downregulated their craving successfully along sensory and affective dimensions (study 1: F(2, 29.843, p<.001); study 2: F(1.14, 43.45, p<.001). The application of the self-control strategy was associated with significantly reduced craving ratings, lower pleasantness ratings and elevated unpleasantness ratings (see table 3).

Table 3: *Overall task-effects in the craving regulation task in study 1 (3) and study 2 (4): mean values and significance as assessed with paired sample t-tests between ratings of the self-control vs. control strategy.*

		Self-control strategy	Control strategy	Significance
Craving	*Study 1:*	2.76	3.17	p<.01
	Study 2:	2.59	3.18	p<.001
Pleasantness	*Study 1:*	2.55	3.31	p<.001
	Study 2:	2.26	3.44	p<.001
Unpleasantness	*Study 1:*	3.13	2.33	p<.01
	Study 2:	3.35	2.18	p<.001

Secondly, we investigated whether behavioral measures of self-control success (craving regulation task) would correlate with the ability to anticipate future interoceptive states (breathing restriction task) (3,4). We conducted a partial correlation analysis along the sensory measures of both tasks which revealed a significant association between self-control success (Δ-craving) and the level of interoceptive prediction (Δ-dyspnea) in both studies (see table 4).

Thus, subjects who were more accurate or who overestimated the intensity of the upcoming breathing restriction were more successful in the downregulation of craving. In study 1 (3), we observed a significant correlation of Δ-craving and |Δ|-dyspnea (i.e., the absolute difference scores), which I, however, could not replicate in study 2 (4) (see table 4). Additional analyses along the affective dimension of both tasks (i.e., unpleasantness and pleasantness) did not reveal any significant associations between the affective dimension of exerting self-control and the degree of emotional interoceptive prediction. However, in both studies, the level of interoceptive prediction (Δ-dyspnea) was significantly associated with scores of the *Self-Regulation Scale* (see table 4). Correlational analyses with the absolute rating values of craving and dyspnea (instead of the difference scores) did not reveal any significant association.

Table 4: *Main results of partial correlation analyses between behavioral measures of the breathing restriction task (Δ-dyspnea, |Δ|-dyspnea), the craving regulation task (Δ-craving) and the Self-regulation questionnaire, as published in study 1 (3) and study 2 (4).*

		Δ-dyspnea	**|Δ|-dyspnea**
Δ-craving	*Study 1:*	r = -.421, p<.01	r = -.352, p<.05
	Study 2:	r = -.344, $p_{one\text{-}sided}$<.05	r = -.205, p>.05
Self-Regulation Scale	*Study 1:*	r = -.303, p<.05	-
	Study 2:	r = -.291, $p_{one\text{-}sided}$<.05	-

Quality-control analyses of respiratory measures recorded during the breathing restriction task in study 2 (4) revealed that the mean volume of CO2 expired did not change significantly between conditions across the task (baseline: 0.26 l/min; anticipation: 0.25 l/min; restriction: 0.24 l/min). However, during the breathing restriction, the inspiratory breathing time increased significantly (baseline: 2.2s, restriction: 3.07s, p<.01), and the breathing frequency decreased significantly (baseline: 14.55/min, restriction: 11.83/min, p<.01).

3.2. fMRI-analysis within tasks I: Breathing restriction task

While in study 1 (3) we obtained only behavioral data, study 2 (4) was conducted in an fMRI scanner to acquire both behavioral and brain-activation data. For the analysis of brain regions activated in the breathing restriction task, I performed ROI-based univariate analyses for the contrast of interest, *anticipation > baseline,* which revealed significant activations in the bilateral anterior dorsal insula and in the left anterior ventral insula (FWE- and FDR-corrected

peak-voxel: p<.05). Whole brain analyses revealed additional activations in the calcarine sulcus, right posterior insula and right TPJ (whole-brain FWE-corrected peak-voxel: p<.05).

To investigate the neuronal underpinnings of participants' ability to predict future interoceptive states, I subsequently computed correlational analyses of significant peak-voxel activations during the anticipation of the breathing restriction with the behavioral difference scores between experienced vs. anticipated body state (Δ-dyspnea, Δ-pleasantness, Δ-unpleasantness). I found a positive correlation between Δ-dyspnea and peak-voxel activation in the right TPJ and in the left ventral anterior insula (latter association not significant after FDR correction; see table 5 for both correlational analyses). Thus, an underestimation of the body state correlated with more activation in the right TPJ and the left ventral anterior insula.

Additionally, I computed correlational analyses of Δ-dyspnea and the slope of signal increase in the anterior insula during the anticipation of the breathing restriction which revealed a significant positive correlation of the slope of the left ventral anterior insula and Δ-dyspnea (see table 5). Thus, a faster signal increase of the ventral anterior insula was linked to an underestimation of the body state.

In addition to these univariate analyses, study 2 (4) included a network-based functional connectivity approach (59,60) conducted by Henrik Walter and colleagues. These analyses revealed that an underestimation of the breathing restriction (i.e., higher values of Δ-dyspnea) was associated with a stronger task-related connectivity of a network including among others the anterior insula, TPJ and regions of the prefrontal cognitive control network (such as vlPFC, dlPFC). On the other hand, an overestimation of the breathing restriction (i.e., lower values of Δ-dyspnea) correlated to a stronger task-related connectivity of a subnetwork including preSMA and TPJ, i.a.

3.3. fMRI-analysis within tasks II: Craving regulation task

ROI-based analyses of the fMRI-data obtained in the craving regulation task of study 2 (4) revealed significant activations in bilateral anterior dorsal insula, vlPFC and bilateral preSMA (FWE-corrected peak-voxel: p<.05). However, when correcting for multiple comparisons (FDR-correction) peak-voxel activations in the anterior dorsal insula and the left preSMA did not remain significant.

To investigate whether brain activations during the downregulation of craving correlated with behavioral measures of self-control, I conducted correlational analyses of significant task-related peak-voxel activations with the difference scores between the self-control condition and

control condition (Δ-craving, Δ-unpleasantness, Δ-pleasantness). These correlational analyses revealed a positive correlation of Δ-craving and activation of the left preSMA during downregulation of craving (not significant after FDR correction, see table 5) as well as significant correlations of activation of bilateral preSMA to Δ-unpleasantness (left: r = -.528, p<.01; right: r = -.588, p<.001) and Δ-pleasantness (left: r = .596, p<.001; right: r = .455, p<.01). Thus, participants who were more successful at downregulating their craving, or who felt less pleasantness and more unpleasantness during the downregulation, showed greater activation in the preSMA. For the craving regulation task, I did not compute the slope of signal increase of the anterior insula, given that the observed activation of the anterior insula in the ROI-based analyses did not remain significant after FDR-correction.

Again, Henrik Walter and colleagues employed the network-based functional connectivity approach to identify task-induced networks during the downregulation of craving whose connectivity would correlate with the degree of self-control success (i.e., Δ-craving). Two networks associated with self-control success were identified: on the one hand, a sub-network including, i.a., the anterior insula and TPJ and, on the other hand, a second network including orbitofrontal and inferior temporal regions.

3.4. Brain-behavior relationship between tasks

Finally, I assessed whether task-specific neuronal activations in one task would also be associated with behavior in the respective other task, indicating the existence of shared brain structures that provide processing advantages across both contexts (4).

First, I investigated whether brain activations during the anticipation of the breathing restriction would correlate with the level of self-control success. I found a significant negative correlation between Δ-craving and the peak-voxel activation of the bilateral dorsal anterior insula during the anticipation of the breathing restriction (not significant after FDR-correction; see table 5). Secondly, I explored whether the level of brain activation during the downregulation of craving would be linked to the degree of interoceptive prediction. I found a significant negative correlation between Δ-dyspnea and activation of the right preSMA during downregulation of craving (not significant after FDR-correction; see table 5).

In conclusion, subjects with more self-control during the craving regulation task exhibited a weaker activation of the dorsal anterior insula during the anticipation of the breathing restriction, while vice-versa, participants who overestimated the breathing restriction, showed a greater activation of the preSMA during the downregulation of craving (however, both associations not significant after FDR-correction).

Table 5: *Summary of main results of correlational analyses conducted between behavioral measures and peak-voxel activations of the breathing restriction and craving regulation task. All results have been published in study 2, see tables 5 and 7 (4).*

Brain activation during tasks		**Δ-dyspnea** (breathing task)	**Δ-craving** (craving task)
Breathing task	*Ventral anterior insula*	L: r =.35, p=.04[1]	n.s.
	Slope of signal increase in ventral anterior insula	L: r =.52, p<.01	n.s.
	Dorsal anterior insula	n.s.	L: r =-.38, p=.03[1] R: r =-.37, p=.03[1]
	TPJ	R: r =.47, p<.01	n.s.
Craving task	*preSMA*	R: r=-.46, p<.01[1]	L: r =.35, p=.03[1]

[1] *not significant after FDR correction due to multiple comparisons; L: left; R: right; n.s.: not significant*

Parallel to the univariate analyses of between-tasks brain-behavior relationship that I conducted, Henrik Walter and colleagues performed network-based analyses to investigate brain-behavior relationships between tasks (4). During the anticipation of the breathing restriction, subjects with stronger connectivity in a network including, i.a., the insula, TPJ and preSMA were more successful in the craving regulation task. During the downregulation of craving, on the other hand, connectivity in a network including, i.a., the insula, TPJ and regions of the cognitive control network was associated with an overestimation of the breathing restriction.

4. Discussion

4.1. Main results

In a behavioral study (3) and an fMRI-study (4), I investigated whether self-control success is linked to subjects' ability to predict future interoceptive states and explored which neuronal processes underpin this relationship between self-control and interoceptive prediction. In both experimental studies, two independent groups of healthy subjects performed the same two tasks: on the one hand, an inspiratory breathing restriction task suitable to measure the anticipation of future aversive body states and, on the other hand, a craving downregulation task to measure self-control success.

In both studies, behavioral measures of self-control and interoceptive prediction were significantly correlated (3,4). Individuals who predicted more accurately or who overestimated

upcoming aversive interoceptive states in the breathing restriction task, were more successful in the downregulation of craving. Moreover, in both studies, a more accurate prediction, or an overestimation of aversive interoceptive states was linked to a higher score on a measure of trait self-control.

In the analyses of fMRI-data in study 2 (4), I observed that the anterior insula and preSMA may partly be responsible for these effects, as they were activated in both tasks. Specifically, I found a significant correlation of interoceptive prediction (i.e., Δ-dyspnea) and the slope of anterior insular activation during the anticipation of upcoming breathing restrictions. The magnitude of anterior insula activation during the anticipation of breathing restrictions was associated with levels of self-control success in the craving regulation task. Furthermore, activation of the preSMA during the downregulation of craving correlated to both self-control success in the craving regulation task and inversely to levels of interoceptive prediction in the breathing restriction task. In line with this, Henrik Walter, second lead author of study 2 (4), and colleagues conducted network-based functional connectivity analyses which revealed that both the preSMA and the anterior insula were engaged in networks associated with self-control and interoceptive prediction.

Taken together, these two studies (3,4) have been the first to present evidence that self-control is directly associated with the prediction of future interoceptive states. Furthermore, based on the univariate activation patterns observed in study 2 (4), I propose that the anterior insula and preSMA partially account for the relationship between self-control and interoceptive prediction.

4.2. Linking self-control to interoceptive prediction

In both studies (3,4), self-control success (i.e., Δ-craving) was only associated with the difference scores of experienced vs. anticipated dyspnea, but not with absolute values. Thus, successful self-control was not related to behavioral measures of how aversive the breathing restriction felt (experienced dyspnea) or how aversive it was expected to be (anticipated dyspnea), but only to the difference between experienced and anticipated dyspnea. Referring to the interoceptive inference framework (13), this difference between experienced and predicted body state is termed prediction error. The brain strives to minimize prediction errors because it can regulate the body better if it is not constantly surprised by incoming sensory information, but already predicts it and is able to prepare for it (16,20). Our brain minimizes prediction errors in different ways: Either it integrates the incoming sensory information into its updated prediction (i.e., perceptual inference) or it initiates an action that brings the body into such a

state that the incoming signals again correspond to the predicted model (i.e., active inference; (13)).

During the anticipation phase of the breathing restriction experiment, the brain prepared itself for the upcoming breathing restriction both actively, e.g., by preparing to take deeper and slower breaths, and perceptually, by incorporating the upcoming sensation of dyspnea in its internal model. Subsequently, when the breathing restriction occurred, the brain could compare its predicted model of the breathing restriction with the incoming interoceptive data regarding the actual experience of the breathing restriction. Thus, if the prediction and the experience of the breathing restriction did not match, a *state prediction error* might have been computed, i.e., a signal informing that the predicted model of the body state with the breathing restriction is inconsistent with the information arising from the body (20).

Since craving downregulation was significantly associated with measures of interoceptive prediction (i.e., Δ-dyspnea), the results of our studies suggest that not only the breathing restriction task but also the craving regulation task relies on the prediction of future interoceptive states and the computation of prediction errors – albeit on a different level (3,4). It has been proposed that in decision-making, individuals predict the interoceptive consequences of possible action outcomes (12,19) – in this case, predicting what effects eating unhealthy snacks will have on the body. The brain then compares these interoceptive predictions with the internal model of the body state that the brain believes it should occupy to ensure survival (13), computes a prediction error between the anticipated action outcomes and the desired state and decides for the option with the smallest *preference* prediction error (20). The results of our study support the hypothesis that individuals need to accurately predict future interoceptive states associated with decision outcomes in order to act in accordance with homeostatic goals (3,4). In the case of our experiments, individuals who had a stronger representation of their future aversive state with the breathing restriction, might also have computed a stronger prediction of the aversive future interoceptive state after eating unhealthy snacks and therefore might have been more successful in self-control.

In study 1 (3), self-control success was associated with both the directed scores of interoceptive prediction (i.e., Δ-dyspnea) and the absolute difference scores (i.e., |Δ|-dyspnea) – although the latter association was weaker. In study 2 (4), I could not replicate the association of self-control with the absolute prediction errors. This implies that only an overestimation of an aversive body state, but not an underestimation, may lead to successful avoidance of actions that counteract homeostasis and thus, successful self-control. As discussed in study 2 (4), these results provide

further evidence for the existence of directed prediction error, i.e., the notion that it makes a difference whether individuals overestimate or underestimate interoceptive signals. For example, recent studies suggest that anorexia nervosa may partly result from an abnormal overestimation of situations that elicit interoceptive changes (50,51), whereas obesity, for example, is characterized by reduced interoceptive sensitivity (61).

4.3. Neuronal substrates underpinning the relationship of self-control and interoceptive prediction

In study 2 (4), I used univariate analyses to investigate brain regions underlying the association between self-control and interoceptive prediction. Specifically, I hypothesized that the anterior insula would be the primary region involved in both craving regulation and anticipation of future aversive states, given its engagement in interoceptive prediction, affective and cognitive predictive processing and self-control (34–36,43). As expected, I observed the involvement of the anterior insula in both tasks, yet the direction of the relationship between behavioral measures and peak-voxel activation in the breathing restriction task was reverse to what I had expected a priori. I had hypothesized that higher levels of both interoceptive prediction and self-control would be accompanied by a stronger activation of the anterior insula. But on the contrary, I found that a stronger anticipation of the breathing restriction as well as more self-control success in the craving task correlated with a lower peak-voxel activation of the anterior insula and a weaker slope of anterior insula activation during the anticipation of the breathing restriction.

As discussed in study 2 (4), this unexpected direction of brain-behavior relationship can be interpreted as a consequence of the different task demands and thus as an indication of different neural efficiency of participants. The *neural efficiency hypothesis* (62) claims that, compared to low-performers, high-performers show reduced brain activation on low-demand tasks but more activation on high-demand tasks. The *neural efficiency hypothesis* has first emerged to explain processing differences among differently intelligent subjects but has subsequently been applied to various domains, including decision-making tasks (63), emotion regulation (64), and movement imagination (65). Applying the *neural efficiency hypothesis* to our two experiments, one would speculate that participants with higher self-control ability would show greater neuronal activation during the high-demanding self-control task, while showing less activation during the passive anticipation of an upcoming breathing restriction than subjects with lower self-control ability (4). The data published in study 2 (4) is consistent with this conclusion: Those who overestimated the breathing restriction showed less engagement of the anterior insula (and TPJ) during the anticipation of the breathing restriction (i.e., reduced anterior insula

slope and TPJ activity, weaker connectivity to preSMA and the cognitive control network) but showed more self-control success in the craving regulation task with more activity of the preSMA and stronger connectivity of the anterior insula and the cognitive control network.

As previously hypothesized (4), I observed that ventral and dorsal parts of the anterior insula accounted for different neuronal processes in the experimental tasks. On the one hand, activation of the anterior *ventral* insula during the anticipation of the breathing restriction was associated with subjects' interoceptive prediction. As discussed in study 2 (4), this result corresponds to recent proposals that the ventral anterior insula serves as a basis for subjective feelings states (41,44) which in turn are computed based on interoceptive information (16). On the other hand, I observed an association between self-control success and peak-voxel activation of the anterior *dorsal* insula during the anticipation of the breathing restriction (not significant after FDR-correction), which is in agreement with recent evidence that activation of the dorsal anterior insula is elicited during cognitive tasks (41) and the development of specific goals (4,44).

As expected (4), the preSMA was activated during the downregulation of craving, and this activation was associated with greater self-control success (i.e., Δ-craving; association not significant after FDR-correction), and greater change of emotions triggered by the downregulation of craving (i.e., Δ-unpleasantness and Δ-pleasantness). Furthermore, preSMA activation during the downregulation of craving was stronger in those subjects who overestimated future aversive interoceptive states (Δ-dyspnea). In line with our findings, a recent meta-analysis proposed the preSMA as a core region of both behavioral and emotional control (36). Further studies highlighted its involvement in dietary self-control (35) and in the generation and selection of complex actions (66). The results of my univariate analyses (4) provide further evidence for the role of the preSMA as a key region of (dietary) self-control. Furthermore, due to its involvement in both the craving regulation task and the breathing restriction task, the preSMA – together with the anterior insula – may play a central role in predicting future aversive interoceptive body states which I consider to be the basis for successful self-control.

Although I speculated that the TPJ would be engaged during the craving regulation task due to its well-established involvement in eating self-control as well as behavioral and emotional control (35,36), the TPJ was not activated during the application of self-control strategies (4). However, I observed whole-brain corrected activation of the TPJ during the anticipation of the breathing restriction, which correlated significantly with Δ-dyspnea, as well as engagement of

the TPJ in Henrik Walter's data-driven functional connectivity analyses across both tasks. As discussed in study 2 (4), activation of the TPJ has not only been reported in the context of self-control, but the TPJ is also considered a central neuronal correlate of the ability to deduce the mental states of others, as coined by the term "theory of mind" (67), which in turn has recently been linked to interoceptive prediction (68). Based on this scientific evidence and the observed strong correlation between TPJ activation and interoceptive prediction during the breathing restriction task, the TPJ might be a hub region involved in mentalizing future interoceptive states (4).

In the network-based functional connectivity approach, Henrik Walter and colleagues found a pattern consistent with the previously described peak-voxel activation of anterior insula, TPJ and preSMA (4). However, while involvement of the anterior insula, preSMA and TPJ corresponded to the a-priori defined regions of interests, the data-driven functional connectivity approach revealed spatially distributed networks spanning a variety of regions that had not been specifically hypothesized beforehand. Therefore, it may be that combined interactions of spatially distributed networks are responsible for interoceptive predictive processing and self-control, with the anterior insula, TPJ and preSMA possibly serving as hub regions of this large-scale network (4). In line with these results, recent theories propose that a network of agranular, limbic cortices such as the anterior insula and the cingulate cortices are at the top of the interoceptive predictive hierarchy (12,69). This network, which connects the default mode network to the salience network, is proposed to encode the internal model and thus determine perception and actions. Research on self-control in turn has also provided evidence that self-control is not enabled by individual brain regions, but that the efficient interaction of regions in a network is necessary (70,71). Future research should thus concentrate on studying large-scale brain networks underlying the relationship between self-control and interoceptive prediction (4).

4.4. Clinical implications

The hypothesis that self-control depends on the successful interoceptive prediction of future body states, has several clinical implications, particularly for psychiatric disorders and eating disorders. Following the results of our studies (3,4), failures of self-control may be promoted by an erroneous prediction and valuation of future body states linked to decision outcomes.

For instance, studies on obesity revealed, on the one hand, reduced interoceptive signaling in obese individuals (61), and on the other hand, lower self-control abilities than in normal-weight individuals (72). Based on our findings, one might speculate that obese individuals cannot

successfully anticipate the aversive state of satiety associated with an interoceptive energy excess and therefore maintain a dysfunctional homeostatic behavior of overeating.

The opposite is true for patients with anorexia nervosa. Anorectic patients are characterized by a disproportionate degree of self-control, not only with respect to food-intake (73). In addition, individuals with anorexia nervosa show an abnormal amplification of anticipatory signals to situations that elicit interoceptive change and, moreover, experience cardiorespiratory illusions (i.e., perception of interoceptive signals without occurred visceral stimuli), especially in a pre-meal state (74). Possibly as a result of the amplified interoceptive sensitivity, subjects with anorexia nervosa maintain a hyper-precise prior belief that food intake induces an aversive interoceptive state (4,75). Consequently, the brain choses starvation to minimize the amplified anticipatory activity towards interoceptive signals, while assigning less precision to allostatic goals. Thus, the brain fails to attend to allostatic goals adequately during action selection, which results in dysfunctional homeostatic and life-threatening eating behavior. Interestingly, recovered anorexia nervosa patients showed insular hypoactivation during the anticipation of breathing restrictions (58) which concurs with my finding that more self-controlled individuals show less activation of the insular cortex during the anticipation of breathing restrictions (4).

Impaired self-control and dysfunctional homeostatic decision-making are a core symptom of drug addiction disorders (76). Moreover, individuals with drug addiction disorders show attenuated processing of aversive interoceptive decision outcomes, which thus fail to update the internal model to guide future behavior (45). As a result, they cannot efficiently anticipate the aversive bodily effects of consuming the drug, so that their decisions rely on the highly learned pleasant effects of drug consumption. The anterior insula is suggested to play a key role in addictive behavior, possibly processing the interoceptive pleasant effects of drug intake to prioritize goal-directed drug seeking (77). Consistent with this finding, insula damage correlates significantly with more disruptions of smoking addiction compared to non-insular brain-damage (78).

Obesity, anorexia nervosa, and addictive disorders are just three examples of psychopathological conditions associated with both altered self-control and altered interoceptive processing. Recent theoretical models even suggest that all psychiatric disorders stem from a maladaptively constituted internal model that necessarily leads to pathological choice behavior (79). In line with this, a meta-analysis of structural neuroimaging studies across multiple psychiatric conditions has revealed that grey matter loss of bilateral insula and the

dorsal anterior cingulate cortex converges across all psychiatric conditions studied, suggesting that these regions represent a shared neuronal substrate for psychiatric disorders (80).

The recent recognition of the importance of altered interoceptive prediction in the pathogenesis of psychiatric disorders is accompanied by the emergence of new therapeutic approaches that aim to normalize interoceptive processing. Although specific research is still lacking, there is promising evidence that therapies that improve interoceptive predictive processing may also improve self-control. One such therapeutic approach is the field of mindfulness-based interventions, defined as practicing awareness of the present moment by adopting a mindset of acceptance and non-judgment (81). Mindfulness has been practiced in Eastern cultures for hundreds of years and has only recently become popular in the West, as a therapy for obesity (82), recurrent depression (83), substance use disorders (84) and anorexia nervosa (85), among others. According to recent theoretical models, mindfulness-based interventions might increase the capacity for perceptual-inference strategies, i.e., the ability to integrate current sensory signals into conscious experience, instead of relying too much on prior expectations (86). In substance use disorders, for example, mindfulness-based interventions might enhance the capacity to accurately register aversive feedback and thus, improve interoceptive predictions of the negative consequences of drug intake. Consistent with our hypothesis that self-control relies on interoceptive prediction, mindfulness-based training has been shown to improve emotion regulation (87), which is an important feature of self-control.

In addition to these therapeutic approaches, interventions such as transcranial magnetic stimulation (88) and deep brain stimulation (89) specifically attempt to normalize aberrant patterns of neuronal activity in targeted brain structures. Although there are already a few promising studies on their efficiency in the treatment of a variety of psychiatric disorders, research is still in its infancy and large high-quality controlled studies are needed to investigate optimal stimulation targets, indications, and risks of these interventions. Based on the results of our study, I suggest that future research should also target the anterior insula and preSMA given that they are potential candidate regions underlying the relationship between interoceptive inference and self-control and could thus be treatment targets for interventions that aim to improve self-control in psychiatric patients.

Another innovative approach to enhance interoceptive processing is real-time fMRI which allows to visualize participants' activation of targeted brain regions in an fMRI scanner in real time and thus enables participants to learn how to self-regulate the activation of these brain regions (90). There is preliminary evidence that real-time fMRI may improve emotion

regulation, a core feature of self-control, in patients with a wide set of psychiatric disorders such as depression, anxiety disorders, schizophrenia and addiction disorders (91). Real-time fMRI has also been proposed to improve self-control in obese individuals (92), however the respective contributions of area-specific mechanisms as well as standardized procedures require further investigation.

4.5. Conclusion

In two studies (3,4) with two independent samples of healthy subjects, we demonstrated a direct link between interoceptive prediction and two measures of self-control (i.e., successful craving reduction and trait self-regulation). Thus, efficient self-control might depend on the ability to anticipate possible decision outcomes as predicted interoceptive states, compare these predicted body states with the internal homeostatic model and choose the option most likely to result in an interoceptive state consistent with long-term homeostatic goals. In univariate analyses of fMRI data obtained in study 2 (4), I demonstrated that the anterior insula and preSMA were recruited in both the interoceptive prediction task and the self-control task and may thus partially account for successful self-control related to the prediction of future interoceptive states. The evidence presented here is potentially promising in explaining why both defective self-control and impaired interoceptive processing are often present in individuals with eating disorders and psychiatric illness. Consequently, our results provide important impulses for new therapeutic approaches that may improve self-control either by enhancing interoceptive processing or by directly stimulating targeted brain areas. However, as these are only the first studies to show the direct behavioral link between self-control and interoceptive prediction, further research is needed to extend our findings and apply them to individuals with psychiatric disorders and their treatment.

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Eidesstattliche Versicherung

„Ich, Anne Kausch-Blecken von Schmeling, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: “Linking Self-control to Interoceptive Prediction – a Behavioral Study and a Functional Magnetic Resonance Imaging Study” bzw. “Der Zusammenhang zwischen Selbstkontrolle und interozeptiver Prädiktion – eine Verhaltensstudie und eine funktionelle Magnetresonanztomographie-Studie” selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe. Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren*innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, statistische Aufarbeitung) und Resultaten werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Erstbetreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte. Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

_____ _____

Ort, Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Publikation 1: Kruschwitz JD, **Kausch A**, Brovkin A, Keshmirian A, Paulus MP, Goschke T, Walter H. Self-control is linked to interoceptive inference: Craving regulation and the prediction of aversive interoceptive states induced with inspiratory breathing load. Cognition. 2019 Dec 1;193:104028.

- Wesentlicher Beitrag bei der Interpretation der Ergebnisse, u.a. Literaturrecherche zur systematischen Einordnung der Ergebnisse hinsichtlich des aktuellen Forschungsstands (siehe *Discussion*)
- Wesentlicher Anteil bei der Erstellung der ersten Version des Manuskripts (v.a. der *Introduction* und *Discussion*) sowie Überarbeitung des Manuskripts

Publikation 2: Walter H*, **Kausch A***, Dorfschmidt L, Waller L, Chinichian N, Veer I, Hilbert K, Lüken U, Paulus MP, Goschke T, Kruschwitz JD. Self-control and interoception: Linking the neural substrates of craving regulation and the prediction of aversive interoceptive states induced by inspiratory breathing restriction. Neuroimage. 2020 Jul 15;215:116841.

**** equal contribution***

- Wesentlicher Anteil bei der konzeptionellen Planung des Studiendesigns, alleinige Erarbeitung des spirometrischen Setups, Erstellung der Online-Fragebögen, Design einer 3D-gedruckten Spiegel-Halterung notwendig für die Durchführung der fMRT-Experimente
- Alleinige Rekrutierung der Proband*innen, E-Mail-Kontakt mit potenziellen Proband*innen zum Screening möglicher Ausschlusskriterien, Führen aller telefonischer Vorgespräche, sowie Koordination der fMRT-Termine
- Durchführung des Briefings der Proband*innen sowie wesentlicher Beitrag bei der fMRT-Datenerhebung als zertifizierter „advanced user“ bei allen fMRT-Terminen
- Alleinige Qualitätskontrolle der spirometrischen Daten, der Verhaltensdaten und der fMRT-Bewegungsparameter (*frame-wise displacement*) mittels SPSS und Matlab
- Alleinige Analyse der Verhaltensdaten (Tab. 8; Abb. 3, 9) sowie der spirometrischen Daten (Tab. 1 des *Supplementary Material*) mittels selbstgeschriebener Matlab-Skripte sowie SPSS
- Hauptverantwortlichkeit für der Definition der *Regions of Interest* (ROIs) für die univariaten fMRT-Analysen nach ausführlicher Literaturrecherche, sowie für die

Erstellung der Masken für die ROI-Analyse mit Hilfe des Brainnetome Atlas und SPM (Tab. 1, 2)

- Hauptverantwortlichkeit für das Preprocessing der fMRT-Daten
- Hauptverantwortlichkeit für die univariaten Analyse der Gehirndaten: alleinige Analyse der peak-voxel Aktivierungen mittels SPM (Tab. 3, 4, 6; Abb. 4, 10), Berechnung der Steigerung der insulären Aktivierung mittels selbstgeschriebenem Matlab-Skript sowie Berechnung der Korrelationen der Gehirndaten mit den Verhaltensdaten mittels SPSS (Tab. 5, 7; Abb. 6, 11, 12, 14-16)
- Wesentlicher Beitrag bei der Interpretation der Ergebnisse, Literaturrecherche zur systematischen Einordnung unserer Ergebnisse hinsichtlich des aktuellen Forschungstands
- Hauptverantwortlichkeit für das Erstellen der ersten Version des Manuskripts, alleiniges Erstellen von Tabellen und Graphiken bezüglich der behavioralen Analysen sowie der univariaten Analysen (s.o.), wesentlicher Anteil an Korrektur und Revision des Manuskripts

_____	_____
Datum	Unterschrift Prof Dr. med. Dr. phil. Henrik Walter (Erstbetreuer)
_____	_____
Datum	Unterschrift Anne Kausch-Blecken von Schmeling

Auszug aus der Journal Summary List für Studie 1

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"PSYCHOLOGY, EXPERIMENTAL"** Selected Category Scheme: WoS

Gesamtanzahl: 85 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	TRENDS IN COGNITIVE SCIENCES	25,391	15.557	0.040790
2	Advances in Experimental Social Psychology	5,133	8.800	0.003330
3	JOURNAL OF EXPERIMENTAL PSYCHOLOGY-GENERAL	10,247	4.107	0.021320
4	DEVELOPMENTAL SCIENCE	6,769	4.078	0.012110
5	Journal of Neuropsychology	582	3.786	0.001340
6	MULTIVARIATE BEHAVIORAL RESEARCH	5,881	3.691	0.006420
7	Behavior Research Methods	14,177	3.597	0.014240
8	COMPUTERS IN HUMAN BEHAVIOR	19,700	3.536	0.033880
9	Social Cognitive and Affective Neuroscience	6,443	3.500	0.020770
10	JOURNAL OF COGNITIVE NEUROSCIENCE	16,920	3.468	0.020380
11	COGNITION	16,694	3.354	0.021700
12	PSYCHOPHYSIOLOGY	13,301	3.118	0.012340
13	COGNITIVE PSYCHOLOGY	7,562	3.104	0.003910
14	PSYCHONOMIC BULLETIN & REVIEW	10,093	3.092	0.016290
15	EMOTION	8,174	3.039	0.013030
16	BIOLOGICAL PSYCHOLOGY	9,081	2.891	0.013510
17	NEUROPSYCHOLOGIA	24,704	2.888	0.028190
18	Wiley Interdisciplinary Reviews-Cognitive Science	1,070	2.881	0.003210
19	INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY	7,496	2.868	0.010950
20	BRAIN AND LANGUAGE	6,499	2.851	0.008280
21	JOURNAL OF MEMORY AND LANGUAGE	8,808	2.829	0.008700
22	Bilingualism-Language and Cognition	2,356	2.707	0.004280
23	COGNITION AND INSTRUCTION	1,854	2.654	0.001660
24	COGNITIVE SCIENCE	5,489	2.617	0.006200

Druckversion der Publikation 1: Kruschwitz JD, **Kausch A**, Brovkin A, Keshmirian A, Paulus MP, Goschke T, Walter H. Self-control is linked to interoceptive inference: Craving regulation and the prediction of aversive interoceptive states induced with inspiratory breathing load. Cognition. 2019 Dec 1;193:104028.

https://doi.org/10.1016/j.cognition.2019.104028

Auszug aus der Journal Summary List für Studie 2

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"NEUROSCIENCES"** Selected Category Scheme: WoS
Gesamtanzahl: 267 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS NEUROSCIENCE	43,107	33.162	0.068480
2	NATURE NEUROSCIENCE	63,390	21.126	0.164700
3	ACTA NEUROPATHOLOGICA	20,206	18.174	0.041660
4	BEHAVIORAL AND BRAIN SCIENCES	9,377	17.194	0.010240
5	TRENDS IN COGNITIVE SCIENCES	27,095	16.173	0.040040
6	JOURNAL OF PINEAL RESEARCH	10,695	15.221	0.010560
7	NEURON	95,348	14.403	0.218680
8	TRENDS IN NEUROSCIENCES	20,163	12.314	0.024480
9	Annual Review of Neuroscience	14,042	12.043	0.015020
10	MOLECULAR PSYCHIATRY	20,353	11.973	0.049290
11	BRAIN	52,970	11.814	0.074030
12	BIOLOGICAL PSYCHIATRY	43,122	11.501	0.053320
13	PROGRESS IN NEUROBIOLOGY	12,929	10.658	0.013230
14	Nature Human Behaviour	1,230	10.575	0.006550
15	SLEEP MEDICINE REVIEWS	6,920	10.517	0.010920
16	ANNALS OF NEUROLOGY	37,336	9.496	0.048630
17	Molecular Neurodegeneration	4,248	8.274	0.011350
18	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	26,724	8.002	0.051580
19	FRONTIERS IN NEUROENDOCRINOLOGY	4,196	7.852	0.005490
20	Neurology-Neuroimmunology & Neuroinflammation	1,996	7.353	0.008220
21	NEUROPSYCHOPHARMACOLOGY	25,672	7.160	0.039090

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
22	Brain Stimulation	5,457	6.919	0.014470
23	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	3,876	6.878	0.006420
24	NEUROENDOCRINOLOGY	5,046	6.804	0.005690
25	NEUROSCIENTIST	4,986	6.791	0.008520
26	BRAIN BEHAVIOR AND IMMUNITY	14,533	6.170	0.025700
27	BRAIN PATHOLOGY	5,263	6.155	0.007880
28	Alzheimers Research & Therapy	3,160	6.142	0.010700
29	JOURNAL OF NEUROSCIENCE	175,046	6.074	0.233460
30	JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM	19,766	6.040	0.028050
31	PAIN	38,312	6.029	0.039070
32	CURRENT OPINION IN NEUROBIOLOGY	15,090	6.014	0.033650
33	Acta Neuropathologica Communications	3,063	5.883	0.014190
34	Translational Stroke Research	1,955	5.847	0.004330
35	GLIA	14,003	5.829	0.018760
36	NEUROIMAGE	99,720	5.812	0.132720
37	NEURAL NETWORKS	13,063	5.785	0.016060
38	NEUROPSYCHOLOGY REVIEW	2,971	5.739	0.003940
39	Molecular Autism	2,107	5.712	0.008000
40	Journal of Neuroinflammation	11,767	5.700	0.023240
41	Multiple Sclerosis Journal	11,501	5.649	0.022750
42	Annual Review of Vision Science	458	5.622	0.003300
43	Neurotherapeutics	4,475	5.552	0.009060
44	Translational Neurodegeneration	810	5.534	0.002420

Druckversion der Publikation 2: Walter H*, **Kausch A***, Dorfschmidt L, Waller L, Chinichian N, Veer I, Hilbert K, Lüken U, Paulus MP, Goschke T, Kruschwitz JD. Self-control and interoception: Linking the neural substrates of craving regulation and the prediction of aversive interoceptive states induced by inspiratory breathing restriction. Neuroimage. 2020 Jul 15;215:116841. *(*equal contribution)*

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Self-control and interoception: Linking the neural substrates of craving regulation and the prediction of aversive interoceptive states induced by inspiratory breathing restriction

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ABSTRACT

Following the interoceptive inference framework, we set out to replicate our previously reported association of self-control and interoceptive prediction and strived to investigate the neural underpinnings subserving the relationship between self-control and aversive interoceptive predictive models. To this end, we used fMRI and a within-subject design including an inspiratory breathing-load task to examine the prediction of aversive interoceptive perturbation and a craving-regulation for palatable foods task to measure self-control. In this current study, we could successfully replicate previous effects with an independent sample (n = 39) and observed that individuals who 'over-estimated' their upcoming interoceptive state with respect to experienced dyspnea (i.e., anticipated versus experienced) were more effective in the down-regulation of craving using negative future-thinking strategies. These individuals, again, obtained higher scores on a measure of trait self-control, i.e. self-regulation to achieve long-term goals. On a neural level, we found evidence that the anterior insula (AI) and the presupplementary motor area (preSMA), which were recruited in both tasks, partly accounted for these effects. Specifically, levels of AI activation during the anticipation of the aversive interoceptive state (breathing restriction) were associated with self-controlled behavior in the craving task, whereas levels of interoceptive prediction during the breathing task were conversely associated with activation in preSMA during the down-regulation of craving, whose anticipatory activity was correlated with self-control success. Moreover, during the self-control task, levels of interoceptive prediction were associated with connectivity in a spatially distributed network including among other areas the insula and regions of cognitive control, while during the interoceptive prediction task, levels of self-control were associated with connectivity in a spatially distributed network including among other regions the insula and preSMA. In sum, these findings consolidate the notion that self-control is directly linked to interoceptive inference and highlight the contribution of AI and preSMA as candidate regions underlying this relationship possibly creating processing advantages in self-control situations referring to the prediction of future internal states.

1. Introduction

"Most powerful is he who has himself in his own power."

- Seneca (Moral letters to Lucilius).

The human ability to exercise self-control, which can be defined as the ability to resist temptation and override impulsive responses in order to behave consistently with our long-term goals (Baumeister et al., 2007; Hassin et al., 2010), has been of fascination to both philosophers and

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scientists since antiquity as it plays a major role in everyday life (Fantham, 2010). In order to attain our long-term goals, we thus need to suppress impulsive responses to immediate rewards or endure aversive events. Our brain therefore needs to anticipate the consequences a decision will have on the body in the future and weigh the benefit from achieving the long-term goal with the immediate reward (Paulus, 2007a). A simple example is the decision to carry water on a strenuous hike on a hot summer's day in anticipation of becoming thirsty later, even though one is not thirsty now and carrying the water increases energy expenditure (Kuhl and Goschke, 1994). However, it remains unclear to this day how our brain uses these representations of internal models of future bodily states (i.e., the ability to accurately anticipate future bodily needs) to resist immediate or short-term temptations allowing us to exert self-controlled behavior.

For survival, our body needs to satisfy physiological needs and avoid harmful events (Paulus, 2007a; Friston, 2010; Barrett, 2017). The concept of "allostasis", simply defined as the process of achieving stability through change, includes the idea that efficient regulation of the body requires anticipating physiological needs and preparing to satisfy them before they arise (Sterling, 2012). To this end, our brain generates an internal model of the body in the world (Seth and Friston, 2016). The internal model is predictive, not reactive, given that it models the world from the perspective of anticipated physiological needs (Barrett, 2017). It resorts to previous experiences as well as receives feedback from all bodily tissues sensed through interoception, i.e. the sense of the physiological condition of the entire body (Craig, 2002). If discrepancies between the anticipated top-down internal model and interoceptive bottom-up processes occur, prediction errors may arise (Owens et al., 2018). Consistent with the free energy principle (Friston et al., 2010), our brain tries to minimize these prediction errors. One way to do so is to initiate actions to make predictions of the internal model consistent with perceptual signals (Gu and FitzGerald, 2014; Barrett and Simmons, 2015; Seth, 2015; Seth and Friston, 2016). Thus, following the interoceptive inference framework, self-controlled behavior can be framed as minimizing prediction errors through active inference with the aim to achieve a concordance of the long-term internal homeostatic model and the incoming signals (Kruschwitz et al., 2019). Consequently, if predicted interoceptive models are inaccurate, behavior inconsistent with our long-term homeostatic goals should result; e.g. in failures in self-control. Based on this framework we previously hypothesized that self-controlled choices should be affected by the degree to which an individual maintains accurate predictive models of his or her own future interoceptive states (Kruschwitz et al., 2019).

Specifically, in a previous behavioral study we set out to investigate this proposed influence of interoceptive predictions on self-controlled choices with two independent experimental paradigms in a within-subject design. First, we set up an inspiratory breathing task suitable to measure predictions about impending aversive interoceptive states (Paulus et al., 2012). Inspiratory breathing restriction is a powerful tool to affect the internal body state by evoking strong sensory and affective reactions that do not easily habituate (Davenport and Vovk, 2009) and to test an individual's ability to anticipate how these interoceptive changes will feel like; i.e., in both the intensity ("what will be sensed") and the affective dimension ("how it will feel") (von Leupoldt and Dahme, 2005). Second, participants completed a self-control task in which they were instructed to reduce their craving for tasty but unhealthy snacks by thinking about the long-term negative consequences of succumbing (e.g. 'I will gain weight') (Kruschwitz et al., 2018a, 2019). In this behavioural study ($n = 51$), we could show that those individuals who were more accurate in predicting their interoceptive state with respect to anticipated versus experienced dyspnea were significantly more effective in the downregulation of craving using negative future-thinking strategies and scored higher on a measure of trait self-control, i.e. self-regulation to achieve long-term goals. Thus, we concluded that individuals with more accurate predictive interoceptive models are better in modulating their craving and thus exert better self-control. However, the neural substrates underlying the observed association of interoceptive predictions and self-control have not been investigated yet. Therefore, in this current study we carried out the same experimental protocols as in Kruschwitz et al. (2019) in an fMRI environment with a new independent sample of healthy individuals to gain insight into the neural mechanism driving our previous observation.

The insula has been considered as the primary interoceptive brain region (Craig, 2003). Interoceptive information from the body culminates in the posterior insula, progresses to the anterior insula (Craig, 2003), which then holds a predicted model of the body in the world that is established on the basis of interoceptive information (Seth, 2013). As the anterior insular cortex (AI) also integrates a multitude of further information from other brain regions such as environmental, motivational, hedonic and social conditions it has been suggested that the AI plays not only a major role in interoceptive processing, but also forms a key element in cognitive and affective processing due to its integrative hub status (Chang et al., 2013; Nieuwenhuys, 2012; Seth, 2013; Namkung et al., 2017). Most importantly, the involvement of the insula has also been shown across a variety of predictive tasks like the anticipation of pleasant and aversive stimuli (Lovero et al., 2009; Carlson et al., 2011; Kruschwitz et al., 2018a), the anticipation of gains and losses (Cho et al., 2013), the down-regulation of craving by future-thinking strategies (Kruschwitz et al., 2018b), as well as in intuitive decision-making-tasks (Dunn et al., 2010; Werner et al., 2013). Thus, due to its critical involvement in the processing of predictive interoceptive information, as well as affective and cognitive predictive processing, we hypothesized that the AI would be a primary neural substrate underlying our previously observed association of interoceptive prediction and self-control. More specifically, we speculated that its engagement would create processing advantages across the inspiratory-breathing-restriction task and the craving-down regulation task, both of which refer to the prediction of future internal states. To examine the involvement of the AI during the two tasks, we used univariate analyses of regional activation and a multivariate task-related network–based functional connectivity approach (Zalesky et al., 2010; Fornito et al., 2012) as a data-driven way to identify its connectivity patterns. We hypothesized to identify thus areas previously implicated in interoceptive processing (anterior and mid-cingulate cortex; Holtz et al., 2012; Stewart et al., 2014; Haase et al., 2015) and self-control (i.e., temporoparietal junction, pre-supplementary motor area, ventrolateral prefrontal cortex, and the dorsolateral prefrontal cortex; Han et al., 2018; Langner et al., 2018; Kruschwitz et al., 2018b).

Taken together, in this current study we set out to replicate the previously demonstrated behavioral association of interoceptive prediction and self-control (Kruschwitz et al., 2019) and hypothesized that level of self-control and accuracy of anticipated interoceptive states would be reflected in the engagement of the AI together with regions of self-regulation (i.e., presupplementary motor area and temporoparietal junction; Han et al., 2018; Langner et al., 2018). Furthermore, we expected that task-specific activation in the interoception task would be associated not only to measured behavior within the same task (breathing restriction) but would also correlate to behavior in the self-control task, indicating its relevance as shared neural substrates creating processing advantages across both contexts. Specifically, as it was suggested (Wager and Barrett, 2017) that functional subregions of the insula provide a differential basis for either subjective feeling states (i.e., ventral AI) or the development of motivational states associated with specific actions (i.e., dorsal AI), we expected that interoception related activity in the ventral AI would be associated to interoceptive feelings experienced during the breathing task, whereas interoception related activity of the dorsal AI would show associations to self-controlled behavior in the craving task. Similarly, we assumed that the level of engagement of cognitive control regions during craving down-regulation would be associated to the degree of interoceptive prediction (here, we did not have specific hypothesis about the association of functional subregions to interoceptive behavior). Third, we hypothesized that the level of ability

to anticipate future bodily states and to exert self-control would also be reflected in altered connectivity patterns incorporating the insula and self-regulation areas across both tasks.

To test our hypotheses and to determine brain regions that may underlie the previously observed association between aversive interoceptive predictive models (inspiratory breathing task) and self-control (craving-regulation task) we followed an a-priori determined analysis scheme for task-activity and task-connectivity analyses. For *task-activity*, we (1) conducted analyses of within-task main effects and determined significant peak-voxel activity of the corresponding contrasts; (2) we examined which significant peak-voxels of the previously determined task main effects showed significant within-task brain-behavior relationships (i.e., correlations to the collected task specific behavioral measures); (3) finally, we used the regions from (1) to compute between-task brain-behavior correlations mirroring the behavioral associations between the inspiratory breathing restriction task and the craving-regulation task. Tables 5 and 7 depict the applied analysis scheme for task-activity with a results summary. In a similar logic, we performed analyses with the *task-connectivity*: (1) we determined task induced network configurations (i.e., sub-networks) being associated to the within-task behavior; (2) determined sub-networks of connectivity related to the behavioral performance in the respective other task. Finally, we determined the set of regions that resulted in parallel in these two layers of analyses (i.e., task activation and task connectivity analyses) and focus our interpretations on these areas (while acknowledging that the association of interoceptive prediction and self-control may be realized through combined interactions of brain regions in distributed networks).

2. Methods

2.1. Participants

Forty-nine healthy individuals from the general population (recruited via email lists and a study database) participated in the experiment. Ten subjects were excluded prior to all analyses due to abnormalities observed during the experimental manipulation check, respiration and fMRI quality control (see 2.9). The final sample included 39 non-smoking adults (18 women, mean age = 27.22 years, range 19–34 years) without self-reported respiratory disease and psychiatric disorder. Additional exclusion criteria included pregnancy and other general MRI contraindications. Participants provided their written informed consent and received an amount of 30€ for their participation. The experiment was approved by the Ethics Committee of Technische Universität Dresden.

2.2. General procedure

The experimental design of this study was a replication of our previous behavioral study (Kruschwitz et al., 2019), with the addition that both experiments (within-subject design) now took place in the fMRI scanner and that breathing parameters were monitored and recorded with a full MRI-compatible spirometric device (ZAN600; NSpireHealth). Before coming to the lab, participants were asked not to eat for 2 h. After consenting to the study, subjects participated in two experimental sessions (experiment 1: inspiratory breathing restriction task; experiment 2: craving regulation task), which were counterbalanced in their order of completion across participants. Following the fMRI session, subjects were asked to complete self-report questionnaires (see below).

2.3. Experimental, statistical and fMRI data analysis software

Experiments were implemented using the Psych-Toolbox (V3.0.13) in Matlab (Matlab R2014a; The Mathworks Inc., Natick, MA, USA). Data analyses of behavioral measures were performed with IBM SPSS Statistics 22. fMRI data were preprocessed with FMRIPREP (Esteban et al., 2019) and standard univariate fMRI data analyses were performed with SPM12 (Statistic Parametric Mapping, Wellcome Department of Imaging Neuroscience, University College London, London, UK) and Matlab. Network-based task-related functional connectivity analyses were performed using the cPPI-toolbox (Fornito et al., 2012) and GraphVar (Kruschwitz et al., 2015). Figures were created with Brain Net Viewer (Xia et al., 2013), SPSS, and the circlize package (Gu et al., 2014) implemented in R (www.R-project.org).

2.4. Functional magnetic resonance imaging

Participants were scanned in a 3T Siemens Tim Trio MRI scanner with a 32-channel head coil. We acquired 161–170 images for each of the three runs of the craving experiment and 452–467 images for each of the two runs of the breathing experiment with 42 axial slices in descending order (varying jitters resulted in differences of total acquisition length). We used a T2*-sensitive one-shot gradient-echo echo-planar imaging (EPI) sequence with the following parameters: repetition time 2490 ms, echo time 25 ms, flip angle 82°, field of view 190 mm, matrix size 76 × 76, voxel size 2.5 × 2.5 × 2.5 mm and inter-slice spacing 2.875 mm. Moreover, we acquired a high-resolution image for spatial referencing with 192 sagittal slices using a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: repetition time 1900 ms, inversion time 900 ms, echo time 2.52 ms, flip angle 9°, matrix size 256 × 256 and voxel size 1 × 1 × 1mm.

2.5. Regions of interest for statistical analyses

Due to its critical involvement in the processing of predictive interoceptive information, as well as affective and cognitive predictive processing, we chose the anterior insula as our primary region of interest (ROI) for both experiments. We hypothesized that the AI would be a primary neural substrate underlying our previously observed association of interoceptive prediction and self-control. As it was suggested that left and right anterior insula engage differentially in interoceptive processing and decision-making (Duerden et al., 2013; Kurth et al., 2010), as well as that functional subregions of the insula provide a differential basis for subjective feeling states (i.e., ventral AI) versus the development of motivational states associated with specific actions (i.e., dorsal AI) (Wager and Barrett, 2017), 4 separate ROIs (left and right ventral and left and right dorsal AI) were used in order to specifically delineate neural activations underlying the investigated process. For the breathing task, we additionally considered the anterior and mid-cingulate cortex as ROIs due to their suggested involvement in interoceptive processing (Holtz et al., 2012; Stewart et al., 2014; Haase et al., 2015). For the craving task, next to the anterior insula, we defined the temporoparietal junction, the pre-supplementary motor area, ventrolateral prefrontal cortex and the dorsolateral prefrontal cortex as ROIs because two recent meta-analyses pointed towards their role in dietary self-control and both, cognitive action control and cognitive emotion control (Han et al., 2018; Langner et al., 2018). All ROIs were derived from the Brainnetome Atlas (Fan et al., 2016; http://atlas.brainnetome.org/). To create the ROIs for standard univariate analyses, we combined several small Brainnetome segments across hemispheres using the ImageCalc function in SPM (see Tables 1 and 2; for insula subregions we used the preexisting masks without modification). For data-driven task-based connectivity analyses, we however made use of the original fine grained parcellation into 246 regions, enabling a more spatially localized detection of effect associated brain networks.

2.6. Summary of the a-priori determined analysis scheme

To test our hypotheses and to determine brain regions that may underlie the previously observed association between aversive interoceptive predictive models (inspiratory breathing task) and self-control (craving-regulation task) we followed an a-priori determined analysis scheme for task-activity and task-connectivity analyses. For task-activity, we (1)

Table 1
Regions of Interest (ROI) for the Breathing task derived from Brainnetome Atlas and combined using the ImageCalc Function in SPM.

ROI number	ROI name	Brainnetome ID	Volume
1	anterior ventral insula L	165	221 voxel
2	anterior ventral insula R	166	189 voxel
3	anterior dorsal insula L	167	251 voxel
4	anterior dorsal insula R	168	256 voxel
5*	anterior and midcingulate cortex L	177,179,183,187	1548 voxel
	anterior and midcingulate cortex R	178, 180, 184, 188	1345 voxel

L = Left; R = Right; * = combined L and R as one ROI.

Table 2
Regions of Interest (ROI) for the Craving task derived from the Brainnetome Atlas and combined using the ImageCalc Function in SPM.

ROI number	ROI name	Brainnetome ID	Volume
1	anterior ventral insula L	165	221 voxel
2	anterior ventral insula R	166	189 voxel
3	anterior dorsal insula L	167	251 voxel
4	anterior dorsal insula R	168	256 voxel
5*	midcingulate cortex L	183	359 voxel
	midcingulate cortex R	184	255 voxel
6*	ventrolateral PFC L	29, 31, 33, 35, 37, 39	1869 voxel
	ventrolateral PFC R	30, 32, 34, 36, 38, 40	2103 voxel
7*	dorsolateral PFC L	15, 19, 21	2601 voxel
	dorsolateral PFC R	16, 20, 22	2731 voxel
8*	preSMA L	1	720 voxel
	preSMA R	2	868 voxel
9*	temporoparietal junction L	121, 123, 135, 137, 139, 141, 143, 145	7152 voxel
	temporoparietal junction R	122, 124, 136, 138, 140, 142, 144, 146	6958 voxel

L = left; R = right; * = combined L and R as one ROI; PFC = prefrontal cortex; preSMA = pre-supplementary motor area.

conducted analyses of within-task main effects and determined significant peak-voxel activity of the corresponding contrasts; (2) we examined which significant peak-voxels of the previously determined task main effects showed significant within-task brain-behavior relationships (i.e., correlations to the collected task specific behavioral measures); (3) finally, we used the regions from (1) to compute between-task brain-behavior correlations mirroring the behavioral associations between the inspiratory breathing restriction task and the craving-regulation task. Tables 5 and 7 depict the applied analysis scheme for task-activity with a results summary. In a similar logic, we performed analyses with the task-connectivity: (1) we determined task induced network configurations (i.e., sub-networks) being associated to the within-task behavior; (2) determined sub-networks of connectivity related to the behavioral performance in the respective other task. Finally, we determined the set of regions that resulted in parallel in these two layers of analyses (i.e., task activation and task connectivity analyses).

2.7. Experiment 1: inspiratory breathing restriction task

2.7.1. Resistive load apparatus

Resistive loads were first introduced by Lopata et al. (1977) and Gottfried et al. (1978) and are airflow-dependent loads (Kifle et al., 1997). The perceived magnitude of externally added loads to breathing is directly dependent on the inspiratory muscle force developed and its duration, and indirectly on the added load (Killian et al., 1982).

For the breathing restriction task, participants breathed through a respiratory mask covering both mouth and nose. The mask was connected to a two-way non-rebreathing valve (Hans Rudolph 2600 Series) ensuring the separation of inspiratory and expiratory air. The resistance load was a linear resistor (Hans Rudolph 7100R-40), which is a passive non-electric pneumatic device providing a constant resistance to air flow of 40 cmH2O/LPS (liters per second), thereby altering subjective symptoms without significantly affecting CO2 or O2 level (Paulus et al., 2012; Haase et al., 2015). A plastic tube (length: 3 m) was connected to the inspiratory side of the non-breathing valve. Breathing restrictions were induced by temporarily inserting the linear resistor into the tube without participants awareness. To assure that CO2 levels stayed constant throughout the experimental session and thus would not influence measured brain activation, we monitored and recorded VCO2-levels in the inspiratory and expiratory air, oxygen levels, inspiratory pressure, inspiratory time, airflow, breathing frequency, and the breathing volume during the experiment.

2.7.2. Experimental procedure

Prior to the experiment, participants were asked to breathe through the respiratory mask with and without the respiratory load for 1 min each and rate their experience in two separate dimensions (sensory dimension: breathing dyspnea; affective dimension: pleasantness and unpleasantness) to establish a baseline.

During the scanning session subjects performed a continuous performance task (CPT; validated for fMRI usage by Paulus et al., 2012) in which they were asked to press buttons corresponding to arrows that were presented for 2 s on the screen (left arrow = left button, right arrow = right button). During the task, the background color of the screen served as a cue to the impending breathing load. In the beginning of each trial the background of the screen was black (12 ± 3s) and subsequently changed its color for 12 s to yellow implying a 1/3 chance of an upcoming 40 s inspiratory breathing load. In case the breathing load appeared, participants were asked after an interim-period (12 ± 3s) to evaluate their experience during breathing restriction in experienced dyspnea ('what is sensed': sensory dimension) as well as in terms of pleasantness and unpleasantness ('how it feels': affective dimensions) on a 5-point Likert scale by moving a cursor using response keys. Each rating scale was presented for 3s. In 2/3 of trials participants did not experience a breathing restriction period after the color-change of the screen, but were asked after a 12 ± 3s interim-period to evaluate their anticipated experience of breathing restriction (i.e. "how they would have felt with breathing loads") on the same three scales. This probabilistic nature of restriction occurrence was implemented to maximize the amount of anticipation trials while keeping the time of the experiment to a minimum. Each trial concluded with an inter-trial interval of 2 ± 1.5s, during which participants saw a fixation cross. Participants completed 2 runs consisting of 36 trials in total (12 restriction trials and 24 non-restricted trials) that were presented in a pseudorandomized order. Each run lasted approximately 19 min (see Fig. 1).

2.7.3. Behavioral measures of interest

To obtain a measure of the level of interoceptive prediction, we computed the difference between the rating of the experienced body-state during breathing restriction and the rating of the anticipated body-state of breathing restriction (termed as Δ-body-state; experienced - anticipated) separately for the three acquired behavioral measures. Specifically, Δ-dyspnea was computed as the difference of the values of perceived dyspnea intensity and anticipated dyspnea intensity. Similarly, we computed Δ-pleasantness and Δ-unpleasantness. Thus, greater negative values of Δ-body-state would refer to an 'over-estimation' of the actual body state (i.e., negative prediction error), whereas greater positive values of Δ-body-state would refer to an 'under-estimation' of the actual body state (i.e., positive prediction error). Importantly, these behavioral measures (dyspnea, pleasantness and unpleasantness) can be

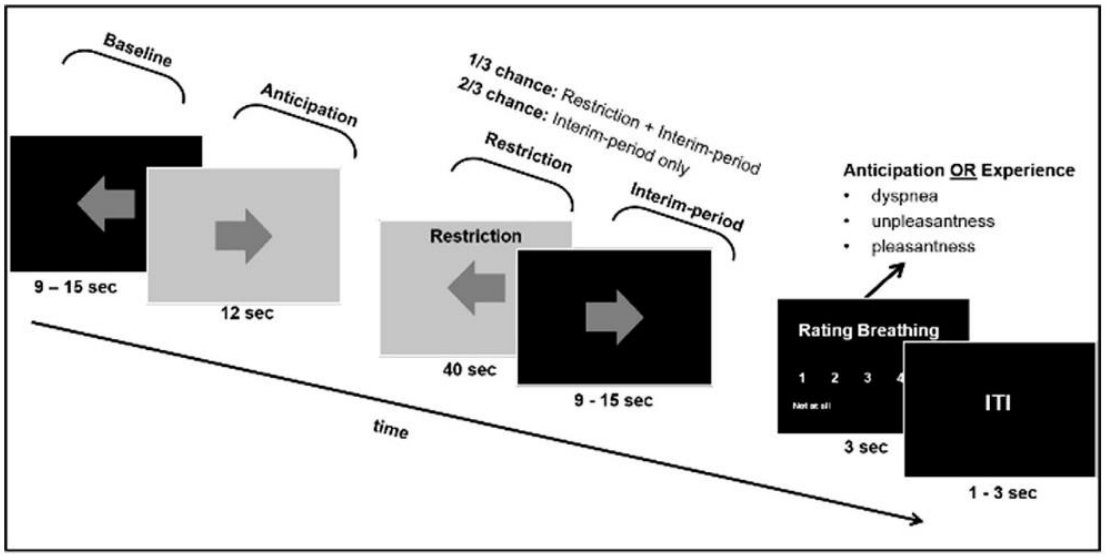

Fig. 1. Trial sequence for experiment 1, in which subjects performed a continuous performance task (CPT, pressing buttons corresponding to arrows). In the beginning of each trial the background of the screen was black and subsequently changed its color for 12 s to yellow implying a 1/3 chance of an upcoming 40 s inspiratory breathing load. In case the breathing load appeared, participants were asked after an interim-period to evaluate their experience during breathing restriction in experienced dyspnea as well as in terms of pleasantness and unpleasantness. In 2/3 of trials participants did not experience a breathing restriction period after the color-change of the screen, but were asked after the interim-period to evaluate their anticipated experience of breathing restriction on the same three scales.

organized along the two established dimensions of respiratory sensations: a sensory dimension, 'what is sensed' (e.g. airflow intensity or dyspnea), and an affective dimension, 'how it feels' (e.g. unpleasantness and pleasantness) (Davenport and Vovk, 2009; von Leupoldt and Dahme, 2005).

2.7.4. Behavioral analyses - overall task effects

We applied two repeated-measure ANOVAs separately for the behavioral variables obtained in the baseline condition (i.e., with and without breathing load: dyspnea, pleasantness, unpleasantness) and for the variables recorded during the continuous performance task (i.e., 'experienced breathing restriction' versus 'anticipated experience of breathing restriction': dyspnea, pleasantness, unpleasantness). We then calculated paired sample t-tests for the post-hoc comparisons of interest in the baseline assessment as well as during the continuous performance task.

2.7.5. fMRI preprocessing

Results included in this manuscript come from preprocessing performed using FMRIPREP version latest (Esteban et al., 2019), a Nipype based tool. Each T1w (T1-weighted) volume was corrected for INU (intensity non-uniformity) using N4BiasFieldCorrection v2.1.0 and skull-stripped using ants Brain Extraction.sh v2.1.0 (using the OASIS template). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c was performed through nonlinear registration with the antsRegistration tool of ANTs v2.1.0, using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using FAST (FSL v5.0.9). Functional data was motion corrected using MCFLIRT (FSL v5.0.9). "Fieldmap-less" distortion correction was performed by co-registering the functional image to the same-subject T1w image with intensity inverted constrained with an average fieldmap template, implemented with antsRegistration (ANTs). This was followed by co-registration to the corresponding T1w using boundary-based registration with 9 degrees of freedom, using FLIRT (FSL). Motion correcting transformations, field distortion correcting warp, BOLD-to-T1w transformation and T1w-to-template (MNI) warp were concatenated and applied in a single step using ants Apply Transforms (ANTs v2.1.0) using Lanczos interpolation. Frame-wise displacement was calculated for each functional run using the implementation of Nipype. ICA-based Automatic Removal Of Motion Artifacts (AROMA) was used to clean up data using the non-aggressive regression setting. Many internal operations of FMRIPREP use Nilearn, principally within the BOLD-processing workflow. Detailed references to the applied procedures can be found here: https://fmriprep.readthedocs.io/en/stable/citing.html.

2.7.6. fMRI analysis - GLM and task related activity

After preprocessing, we constructed a general linear model (GLM) for each participant. Task regressors were convolved with the SPM12 canonical hemodynamic response function. Intrinsic autocorrelations were modeled by a first-order autoregressive model. Low frequency oscillations were removed with a high-pass filter with a cut-off frequency at 1/128 Hz. For the GLM, data was modeled for the three regressors of interest (baseline, anticipation and breathing restriction). The interim-period (i.e., post-restriction/post-non-restriction), the rating period, and the inter-trial-interval were modeled as additional regressors of no interest. Furthermore, we included the six motion regressors in the GLM as well as the time points of either left or right button press and two continuous respiratory measures (i.e., expiratory CO2 volume (VCO2) and airflow (l/s), one measure per TR) resulting in 10 regressors in total. We then computed the contrast of interest as '*anticipation condition* > *baseline condition*' (for completeness the supplementary material also shows results for the remaining contrasts '*anticipation* > *breathing restriction*', as well as '*breathing restriction* > *anticipation*').

We then performed ROI-based and whole-brain one-sample t-tests for each of these contrasts. Significance was assessed as follows: for ROI-based as well as whole-brain analyses we applied a family wise error (FWE)-corrected statistical threshold of $p < .05$ (peak-level), which has been shown to be an appropriate correction method (Eklund et al., 2016). For ROI-based fMRI analyses no cluster-extent threshold was used in addition to the (FWE-corrected, small volume correction; SVC) voxel peak-level thresholding. To control the false discovery rate (FDR, Benjamini and Yekutieli, 2001) due to multiple testing across ROIs, we adjusted the ROI specific FWE-corrected peak-voxel p-values with the probabilities of all observations across ROIs (i.e., peak-voxel

FWE-corrected p-values). A probability of 1 was assigned to ROIs in which we did not observe supra-threshold voxels for their inclusion into FDR adjustments of the remaining observations. Subsequently, we extracted the peak-voxel activation (first eigenvariate adjusted for the effect of interest using the exact same group-level peak-voxel coordinate for every subject) of those regions that survived both controlling procedures (i.e., peak-voxel small volume FWE-correction and the global FDR correction) for the contrast of interest ('*anticipation* > *baseline*'). We then correlated the peak-voxel activation with the behavioral measures of interest in the two independent domains (sensory domain: dyspnea; affective domain: pleasantness and unpleasantness) and subsequently applied FDR correction (Benjamini and Yekutieli, 2001) to these results.

Additionally, for the significant ROIs of ventral and dorsal anterior insula we computed a slope-based analysis using the cPPI derived (see 'functional connectivity analyses' below) time-series signals for the anticipation condition. Specifically, we hypothesized that not only the relative signal increase as captured by regular contrast analysis would entail information about the processing of predicted interoceptive information within the anterior insula, but that also the temporal dynamics of signal increase may contribute to the allocation of the interoceptive predictive model (see Berner et al., 2018 for a similar approach). An interim result generated by the cPPI toolbox are regional time courses derived by extracting the average time-series across all voxels in a region (first eigenvariate; adjusted for the effect of interest; regions here: Brainnetome segments), which are subsequently corrected for confound signals (here: 6 movement parameter, VCO2, and airflow l/s). Using these noise-corrected time series, we defined the slope of signal increase between time points A and B as (y2-y1)/(x2-x1), with A(x1,y1) as the minimum signal intensity in the anticipation regressor, and B(x2,y2) as the maximum signal intensity in the regressor. The final measure was derived by computing the mean across the anticipation conditions and was respectively used to perform correlational analyses with the behavioral measures of interest as described in the previous paragraph.

In both brain-behavior analyses, we included the breathing baseline measures (respectively for each dimension), physical exercise scores (BSA, Fuchs et al., 2015), and age as covariates of no interest. The decision to include these measures as covariates was based on previous literature pointing towards their influence on the sensation of respiratory changes (Kruschwitz et al., 2014).

2.7.7. *fMRI analyses - functional connectivity analyses*

We performed a network-based task-related functional connectivity approach (Fornito et al., 2012; Zalesky et al., 2010) to investigate if we could identify a task induced network configuration (i.e., sub-network) during the anticipation of future aversive interoceptive states that would specifically relate to the level of interoceptive predictions. For this purpose we extracted regional time courses of 246 regions (Brainnetome Atlas; Fan et al., 2016) from the preprocessed task-data and subsequently performed a task-related functional connectivity approach using the correlational psychophysiological interaction (cPPI) methodology described in Fornito et al. (2012). Specifically, task-related network interactions were estimated using a cPPI approach that used partial correlations to isolate covariations in task-related modulations of network activity as distinct from task-unrelated connectivity, noise, and coactivation effects. This analysis resulted in a connectivity matrix (246 × 246) for the contrast of interest '*anticipation* > *baseline*' per subject. An interim result generated by the cPPI toolbox are noise-corrected regional time series (corrected for 6 movement parameter, VCO2, and airflow l/s) that we used for the slope-based temporal dynamic analysis of insular signal in the anticipation condition (see above). Subsequently, for identification of a subnetwork (i.e., graph component) associated with the level of interoceptive prediction (i.e., Δ-dyspnea), we applied the network-based statistics (NBS) approach (Zalesky et al., 2010) as implemented in GraphVar (Kruschwitz et al., 2015) in which we entered the connectivity matrices for all subjects and scores of their corresponding task-behavior in a GLM (covariates of no interest: breathing baseline measures, physical exercise scores, and age). To estimate the null-distribution of maximal graph component size (i.e., to control the FWE rate of the graph component), we used a permutation-based non-parametric approach with 1000 random permutations. To derive sets of supra-threshold links (i.e., the effect associated subnetwork) we decreased the initial-link threshold (start at $p = .05$) until a significant localized sub-network emerged. Graph components were considered significant with $p < .05$ FWE-corrected.

2.8. *Experiment 2: craving regulation task*

2.8.1. *Experimental procedure*

Participants were asked not to eat for 2 h before coming to the lab and completed a cognitive emotion regulation task that has been successfully implemented in the behavioral study of Kruschwitz et al. (2019). During the experiment, pictures of different snacks were presented to the participants. Participants were instructed that they should either apply a self-control-strategy or a imagine-the-taste -strategy (i.e., control condition) while looking at the stimuli. The stimuli were selected based on their ability to induce craving and validated in a previous study (Ludwig et al., 2014). In the self-control strategy participants were instructed to regulate their craving by thinking about the negative long-term consequences of repeatedly consuming snacks (e.g., "I will become obese" or "I will have bad teeth"). In the control condition, they were asked to not regulate but to anticipate the rewarding nature of the stimulus itself. This was done in a within-subject design with all participants applying both conditions. Each condition included pictures of 6 snacks, which were always presented for the same condition within one participant, as the conditions were expected to become associated with the specific snack types. Within participants, the assignment of the snacks to the two conditions was pseudorandomized to exclude bias produced by the specific stimuli. Each strategy was encoded by two distinct visual cues and memorization of the cues was verified by a quiz before the scanning session. Additionally, to train for the experimental session, participants performed 12 training trials of the regulation task on a different set of snacks outside of the scanner.

Next, the experimenter verified that participants understood and were able to apply the strategies during the experiment. Participants were then prepared for the fMRI assessment. In the fMRI scanner but prior to the start of the experiment, participants rated their craving in response to 36 photographic images of unhealthy snack items on a 5-point Likert scale to establish a baseline. From the 36 stimuli, only 12 snacks of the 24 snacks with highest craving rating were subsequently used in the experiment, whereas the highest 6 snacks were assigned to the self-control condition to maximize experienced temptation (the other 6 snacks were assigned to the control condition).

Finally, participants completed 3 runs of the experiment akin to the training session. Each run consisted of 24 trials each (12 trials per condition) that were presented in a pseudorandomized order. In each trial, we first instructed participants to use either the self-control strategy or the control condition using the respective abstract visual cue (2s). After the cue, an image of a snack was presented for 6 ± 1s, during which the participants applied the strategy. After each trial, participants rated either their amount craving for the snack ('what is sensed') or 'how they felt' during application of the strategy (i.e., both unpleasantness and pleasantness elicited by thinking about the negative long-term consequence) on a 5-point Likert scale by moving a cursor using response keys (i.e., 24 ratings per question across all trials and runs). The rating scale was presented for 3s. Each trial concluded with an inter-trial interval of 5 ± 1s, during which participants saw a fixation cross (see Fig. 2). The whole fMRI-experiment lasted 25 min.

2.8.2. *Behavioral measures of interest*

To obtain a measure of self-control success, we computed the difference of respective craving ratings between the self-control condition and the control condition (termed as Δ-craving; control condition > self-

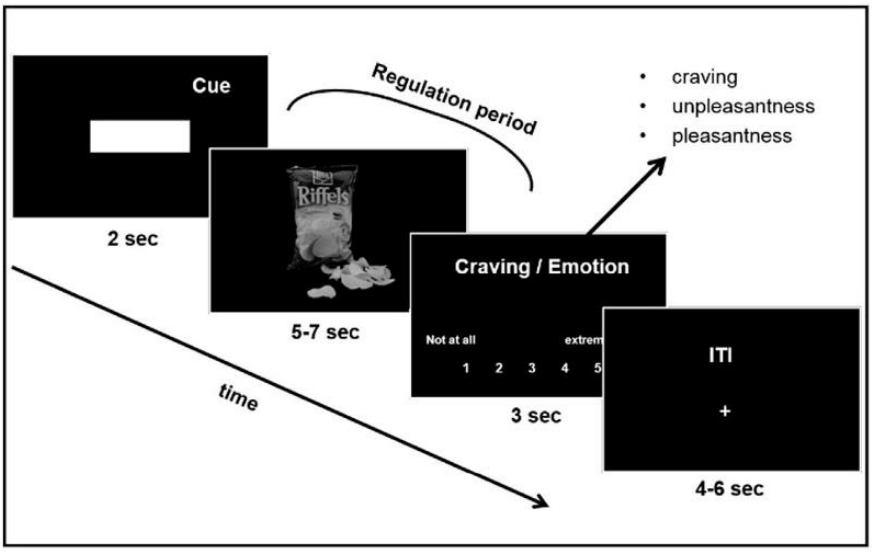

Fig. 2. Trial sequence for experiment 2 with cues indicating either to regulate the craving by thinking about the negative long-term consequences of repeatedly consuming the snacks (e.g., "I will become obese") or to not regulate, but to anticipate the rewarding nature of the stimulus itself (control condition).

control). Similarly, to obtain a differential measure of emotions activated during the self-control strategy, we computed Δ-emotion (i.e., Δ-unpleasantness and Δ-pleasantness; control condition > self-control). In congruency with the two dimensions of respiratory sensations (sensory dimension: 'what is sensed'; affective dimension: 'how it feels'; Davenport and Vovk, 2009; von Leupoldt and Dahme, 2005) and our previous study (Kruschwitz et al., 2019), we assigned the behavioral measures to these two dimensions: experienced emotions elicited by thinking about the negative long-term consequence during application of the self-control strategy as 'how it feels' (i.e., affective dimension) and the amount of craving experience as 'what is sensed' (i.e., sensory dimension).

2.8.3. Behavioral analyses - overall task effects

First, we made sure that the initial assignment of highly craved snacks to the self-control condition was successful and carried out a paired sample *t*-test between the craving ratings of the experimental conditions obtained before the craving regulation experiment (i.e., *self-control > control condition*). To assess the general effect of the self-control task, we applied a repeated-measures ANOVA including the acquired behavioral data (i.e., within-subject factors: "condition" with 2 levels, "rating dimensions" with 3 levels). We then calculated paired sample t-tests for the post-hoc comparisons of interest between the self-control and the control condition (i.e., craving, pleasantness, unpleasantness).

2.8.4. fMRI analysis - GLM and task related activity

All volumes were preprocessed as in experiment 1. Condition cue and image presentation were combined and modeled by a separate regressor for each strategy that lasted $2 + 6 \pm 1$ s. The rating period after the image presentation and the inter-trial intervals were modeled as two separate regressors of no interest. We included six motion regressors in the GLM to correct for motion-related effects. We then calculated the contrast of interest capturing the self-control-network as '*self-control condition > control condition*' in each participant. For completeness, the results of the reverse contrast ('*control condition > self-control condition*') are shown in the supplementary material. We performed group-level analyses and analyses of brain self-report relationship on these contrasts as in experiment 1 (the slope-based temporal dynamic analysis of insular signal in the anticipation condition was not performed because its activation did not remain significant after global FDR correction for the number of peak-voxel across ROIs; see Table 7).

2.8.5. fMRI analyses - functional connectivity analyses

Network-based task-related functional connectivity analyses were conducted as in experiment 1, with modelling the contrast '*self-control condition > control condition*' as the contrast of interest in the cPPI analysis. Specifically, we were interested if we could identify a task induced network configuration (i.e., sub-network) during the down-regulation of craving to palatable foods via negative future thinking strategies that would specifically relate to the level of self-control success (i.e., the amount of regulated craving).

2.9. Self-report questionnaires

After completing the two fMRI experiments, participants completed the *Self-Regulation Scale* (Schwarzer et al., 1999) and the *Physical Activity, Exercise and Sport Questionnaire* (BSA, Fuchs et al., 2015), of which the latter was included as a covariate of no interest in the statistical models in the breathing task due to potential associations of physical fitness and sensation of respiratory changes (Kruschwitz et al., 2014).

2.10. Quality control

To examine if participants performed the tasks correctly, we carried out several experimental manipulation checks on the behavioral data. Specifically, we identified and excluded subjects that did not show any variation in their rating behavior (i.e., did not move the cursor using response keys in experiment 1 or 2) and second, identified and excluded individuals that reported significantly elevated craving ratings in the self-control condition as compared to the control condition in the craving regulation task (using within subject paired sample t-tests with $p < .05$). Additionally, subjects were identified as outliers if the values of Δ-dyspnea in the inspiratory breathing task were either $< Q1 - 1.5 * IQR$ (interquartile range) or $> Q3 + 1.5 * IQR$ (Tukey, 1977). We assumed that those subjects misunderstood the task and rated the experience of absent breathing restriction instead of the anticipated experience of breathing restriction. Consequently, nine subjects (four subjects based in QC in the inspiratory breathing task; five subjects in the craving task) were excluded prior to analyses with the assumption that they either did not follow task instructions, or mixed up the condition cues, or reversed the rating scales, or misunderstood the task. Notably, as individuals remained in the sample, which did only minimally regulate their craving

to the amount of craving as experienced in the control condition, this exclusion does not drive overall task effects to the expected direction but only identifies outlier. In addition to these behavioral exclusion criteria, we evaluated the amount of head movement based on the mean framewise displacement in each run in the fMRI data. One additional subject had to be excluded due to mean framewise displacement >0.5 mm in one run. In total, ten participants were excluded resulting in the final reported sample size of n = 39 subjects.

During the QC-process, we also examined the recorded continuous breathing measures. Specifically, we plotted the inspiratory time (t_insp), inspiratory pressure (mbar) (Pm_insp), breathing frequency (BF), tidal volume (amount of air inhaled) in liters (VT), minute volume (l/min) (VE), airflow (l/s), volume of CO2 expired (l/min) (VCO2), end-tidal CO2 partial pressure (mmHg) (PetCO2) and visually inspected if the spirometric data were recorded continuously and comprehensively. Next, we calculated means of the obtained measures (Pm_insp, t_insp, BF, VT, VE, airflow, VCO2, PetCO2) for the three conditions *baseline, anticipation* and *restriction* and compared them on a group-wise level using two-sample t-tests (anticipation > baseline, restriction > baseline; significance was indicated by p < 0,05). As demonstrated in previous studies (e.g., Haase et al., 2015) levels of VCO2 and PetCO2 did not change significantly between conditions across the task, whereas t_insp, BF, VT, VE and airflow to changed significantly as a function of condition (see supplementary material; Suppl. Table 1).

2.11. Behavioral analyses across tasks - association of self-control and interoceptive prediction

In line with our previous study (Kruschwitz et al., 2019) and in order to replicate that levels of self-control (experiment 2: craving regulation task) would be associated with the degree to which an individual maintains predictive models of his or her own interoceptive state (experiment 1: inspiratory breathing load task), we subdivided both, the experience of inspiratory breathing restriction and the experience of craving into an intensity/sensory dimension (i.e. level of perceived dyspnea and amount of craving experience) and an affective dimension (pleasantness and unpleasantness). According to this categorization, we performed three partial correlation analyses along the dimensions of sensory and affective experience respectively, whereas we specifically focused on the sensory dimension and the previously observed negative association between Δ-craving and Δ-dyspnea. For completeness of the replication, we additionally examined the affective dimension 'Δ-unpleasantness craving regulation' versus 'Δ-unpleasantness breathing restriction' and 'Δ-pleasantness craving regulation' versus 'Δ-pleasantness breathing restriction' for which we however observed null-results in our previous study. In these analyses, we included the breathing baseline measures (respectively for each dimension), physical exercise scores (BSA, Fuchs et al., 2015), and age as covariates of no interest. As a secondary measure we computed the absolute values of the difference scores |Δ| because simple Δ also resulted in negative values for some individuals. Note that simple Δ captures directed prediction errors (i.e., including 'over' versus 'under-estimation' of the body state), whereas |Δ| is a measure of interoceptive prediction accuracy. Based on the a-priori knowledge of the negative association between Δ-craving and Δ-dyspnea

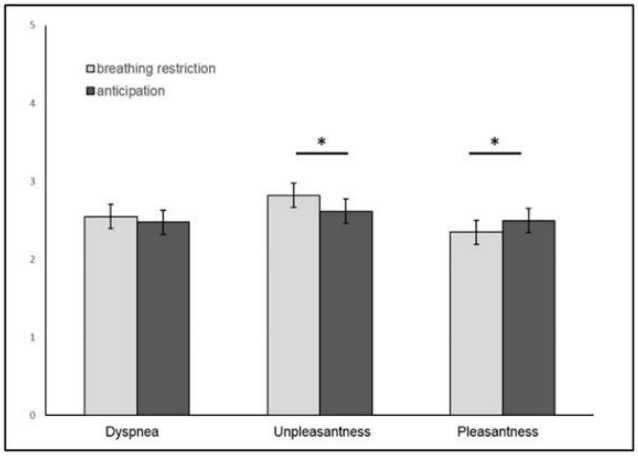

Fig. 3. Overall task-effects in the inspiratory breathing load task (experiment 1). * Post-hoc paired sample t-tests with p < .01. Error-bars represent standard error of the mean (see main text for CI's of difference scores).

(c.f., Kruschwitz et al., 2019), we applied a one-sided test. For the additional 2 partial correlation analyses in the affective dimension, for which we previously observed null-effects, we applied two-tailed testing as the direction of a potential association was unclear. Second, to replicate if the observed effect would again translate to a measure of trait self-control (as opposed to measured self-control success by down-regulation of craving), we computed a partial correlation analysis between scores of the Self-Regulation Scale (Schwarzer, 1999) and Δ-dyspnea with the same covariates as described above. Again, we applied one-tailed testing due to the expected direction of the effect as observed in Kruschwitz et al. (2019). Third, to replicate that the observed associations would solely depend on the differences scores (i.e., Δ), the previous analyses were repeated with the absolute rating values for dyspnea and craving (i.e., not the difference scores). As in our previous study, to provide a complete picture of the underlying data structure and independent of the above introduced classification into 'what is sensed' and 'how it feels', we computed pairwise partial correlations between all difference measures (i.e., Δ) derived from both experiments (i.e., nine possible comparisons) and applied FDR correction (Benjamini and Yekutieli, 2001).

2.12. Analyses of brain behavior relationship across tasks

Based on the behavioral association of interoceptive prediction and self-control that we observed between the two tasks, we were further interested if task-specific neural activations (i.e., in response to self-control or interoception) would be associated not only to measured behavior within the same task but would also correlate to behavior in the respective other task, indicating neural components that would potentially create processing advantages across both contexts. Similar as in the brain-behavior analyses within tasks (task-related *activity*), we now correlated significant peak-voxel activations (derived from task specific

Table 3
Results of experiment 1: ROI analyses with voxel-wise one-sample *t*-test for the contrast 'anticipation > baseline' (n = 39).

ROI number	ROI name	Cluster size	Peak-voxel activity			*p* – peak voxel FWE	FDR corrected *p* for the number of peak-voxel (i.e., 6 across ROIs)
			x	y	z		
1	anterior ventral insula L	9	−33	8	−15	0.015	0.035
		3	−29	20	−5	0.023	0.035
2	anterior ventral insula R	–	–	–	–	1*	1
3	anterior dorsal insula L	8	−31	22	−3	0.017	0.035
4	anterior dorsal insula R	8	34	24	−5	0.006	0.035
5	anterior and midcingulate cortex LR	–	–	–	–	1*	1

FWE: family wise error corrected; FDR: false discovery rate; * a probability of 1 was assigned to ROIs without supra-threshold voxels for inclusion into FDR adjustments.

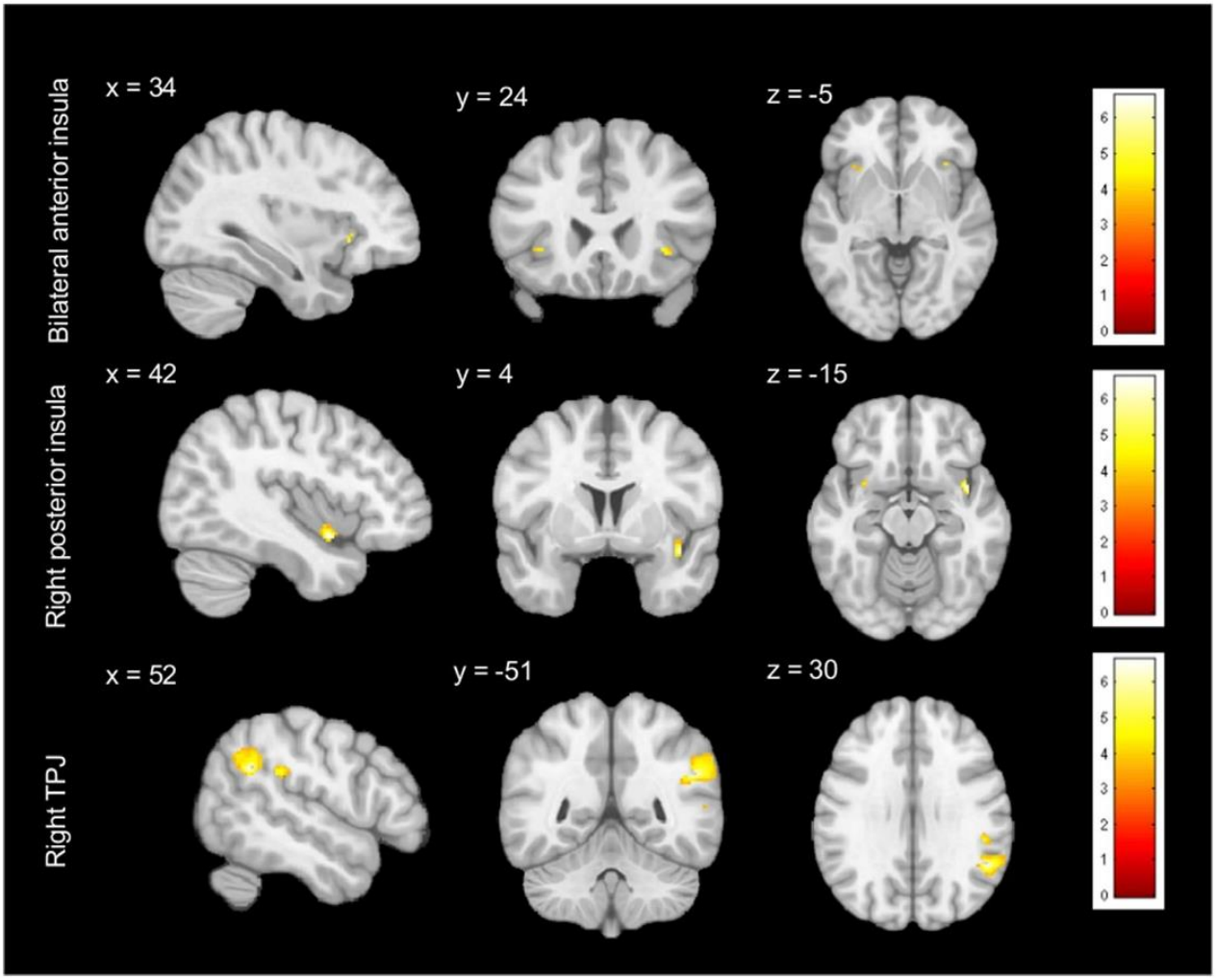

Fig. 4. Main effects in the inspiratory breathing task - ROI-based analyses for the contrast of interest '*anticipation* > *baseline*' revealed significant activations in the bilateral anterior dorsal insula (small-volume FWE-corrected peak-voxel: $p < .05$; Table 3; coordinates of right anterior dorsal insula) and in the left anterior ventral insula (small-volume FWE-corrected peak-voxel: $p < .05$; Table 3; not shown in Figure). Whole-brain analysis revealed additional activations in the right posterior insula and in the right TPJ, specifically in the right angular gyrus of the inferior parietal lobule (all whole-brain FWE-corrected peak-voxel: $p < .05$; Table 4).

ROI-analyses) and slopes of signal increase in the insula (breathing task) with the behavioral data of interest as measured in the respective other task (i.e., Δ-craving or Δ-dyspnea). This approach allowed to answer the following two questions: (1) is the level of anticipatory brain activity in response to an aversive interoceptive state (breathing task - fMRI) associated with level of self-control success (craving regulation task - behavior) and (2) is the level of brain activity during down-regulation of craving (craving task - fMRI) associated with levels of interoceptive prediction (breathing task - behavior)?

Following the same logic, we performed cross-task analyses with the task-related functional *connectivity* measures. To do so, we again applied

Table 4
Results of experiment 1: Whole-brain analyses with voxel-wise one-sample *t*-test for the contrast 'anticipation > baseline' (n = 39).

Brain region	L/R	Cluster size	Peak-voxel activity			*p* – peak voxel FWE
			x	y	z	
posterior insula	R	58	42	4	−15	0.017
angular gyrus (part of TPJ)	R	398	52	−51	30	0.041
calcarine cortex	R	3369	12	−75	10	<0.001

FWE: family wise error corrected; TPJ = temporoparietal junction.

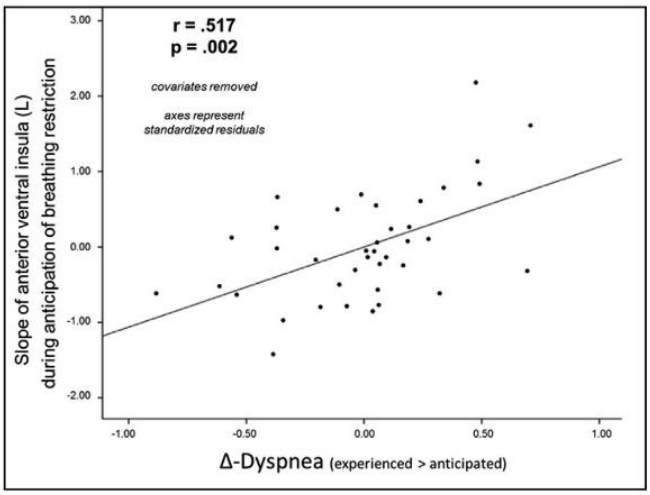

Fig. 5. Brain-behavior analyses revealed a significant positive correlation of Δ-dyspnea and the slope of ROI mean signal increase in the left anterior ventral insula during anticipation of the impending breathing restriction. Thus, a faster signal increase during anticipation was associated with an 'under-estimation' of the body state (i.e., positive prediction error).

Table 5
Results summary of the applied analysis scheme for the layer of task activity in experiment 1 (breathing task) and the associated between-task brain-behavior correlational analysis (c.f. *results* section 3.4).

		Within-task activity (Tables 3 and 4)			Within task brain-behavior correlation for dyspnea (Suppl. Table 5)			Within task brain-behavior correlation for pleasantness and unpleasantness (Suppl. Table 5)		Between-task correlation with craving (Suppl. Table 8 and Fig. 19)	
	Brain region	Exploratory p (within ROI peak-voxel FWE-correction)	FDR corrected p for the number of peak-voxel (6 across ROIs) or whole-brain FWE corrected p	Insula slope extraction (ROI average) if insula survived FDR correction	Correlation targets (9 in total)	Exploratory p (uncorrected)	FDR corrected p (9 comparisons)	Exploratory p (uncorrected)	FDR corrected p (18 comparisons)	Exploratory p (uncorrected)	FDR corrected p (12 comparisons: 9 breathing plus 3 craving)
ROI	anterior ventral insula L (first peak L)	☑ p = .015	☑ p = .035	☑	peak	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	anterior ventral insula L (second peak L)	☑ p = .023	☑ p = .035		peak	☑ dyspnea p = .04	n.s.	n.s.	n.s.	n.s.	n.s.
					slope (ROI mean)	☑ dyspnea p = .002	☑ dyspnea p = .019	☑ pleasantness: p = .008; unpleasantness: p = .035	n.s.	n.s.	n.s.
	anterior ventral insula R	n.s.	n.s.	–	–	–	–	–	–	–	–
	anterior dorsal insula L	☑ p = .017	☑ p = .035	☑	peak	n.s.	n.s.	n.s.	n.s.	☑ p = .029	n.s.
					slope (ROI mean)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	anterior dorsal insula R	☑ p = .006	☑ p = .035	☑	peak	n.s.	n.s.	n.s.	n.s.	☑ p = .031	n.s.
					slope (ROI mean)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	anterior and midcingulate cortex LR	n.s.	n.s.		–	–	–	–	–	–	–
Whole brain	posterior insula	–	☑ p = .017		peak	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	angular gyrus (part of TPJ)	–	☑ p = .041		peak	☑ dyspnea p = .005	☑ dyspnea p = .024	n.s.	n.s.	n.s.	n.s.
	calcarine cortex*	–	☑ p < .001		–	–	–	–	–	–	–

FWE: family wise error corrected; FDR: false discovery rate; TPJ = temporoparietal junction; *activation in the visual cortex was not considered as being relevant for interoceptive processing and further brain self-report analyses.

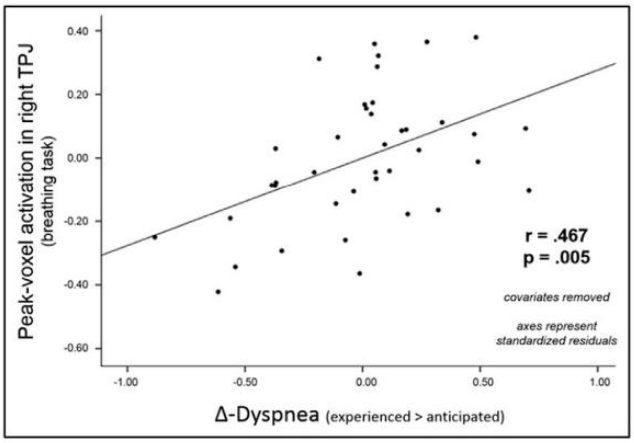

Fig. 6. In the inspiratory breathing restriction task (experiment 1) we observed a significant association between level of interoceptive prediction (i.e., Δ-dyspnea as the difference of perceived dyspnea and anticipated dyspnea) and peak-voxel activation of the right TPJ (TPJ = temporoparietal junction). Hence, an 'under-estimation' of the body state (i.e., positive prediction error) was associated with more activation in TPJ.

the NBS approach (Zalesky et al., 2010) in which we now entered the connectivity matrices for one task and the behavioral scores of the respective other task in a GLM (i.e. Δ-craving or Δ-dyspnea). This approach allowed to answer the following two questions (1) is there a subnetwork during the anticipation of the aversive interoceptive state (breathing task - fMRI) that is associated with levels of self-control success (craving regulation task - behavior) and (2) is there a subnetwork during the down-regulation of craving (craving task - fMRI) that is associated to levels of interoceptive prediction (breathing task - behavior)?

In parallel to the behavioral cross-task analyses, we included the breathing baseline measures (respectively for each dimension), physical exercise scores (BSA, Fuchs et al., 2015), and age as covariates of no interest in the cross-task activation and cross-task network based statistics analyses.

3. Results

3.1. Experiment 1: inspiratory breathing restriction task

3.1.1. Behavioral results - overall task effects

During baseline there was a significant interaction between condition and rating with $F(1.64,62.33) = 101.9$, $p < .001$ (Huynh-Feldt corrected). Specifically, post-hoc paired sample t-tests between loaded breathing and breathing without breathing load revealed that participants experienced elevated levels of dyspnea (no load = 1.76, SE = 0.12; with load = 3.03, SE = 0.16; 95% CI: 1.53, −1,01; $p < .001$) and unpleasantness (no load = 2.47, SE = 0.13; with load = 3.49, SE = 0.14; 95% CI: 1.26, −0.77; $p < .001$), while reporting reduced levels of pleasantness during the load (no load = 3.0, SE = 0.13; with load = 1.94, SE = 0.12; 95% CI: 0.83, 1.29; $p < .001$). Similarly, for behavioral measures acquired during the continuous performance task, we observed a significant interaction effect of condition*rating dimension with $F(1.44,54.81) = 8.61$, $p < .001$, Greenhouse-Geisser correction was applied due to a violation of the assumption of sphericity. Specifically, post-hoc paired sample t-tests between 'anticipated experience of breathing restriction' and 'experienced breathing restriction' revealed that participants anticipated unpleasantness as less intense as compared to the actual experience (anticipation = 2.62, SE = 0.15; actual = 2.82, SE = 0.15; 95% CI: 0.32, −0.09; $p < .01$), while anticipating more pleasantness than actually experienced (anticipation = 2.5, SE = 0.15; actual = 2.35, SE = 0.15; 95% CI: 0.04, 0.25; $p < .01$). The anticipation and the actual experience of dyspnea did not differ significantly (anticipation = 2.48, SE = 0.16, actual = 2.55, SE = 0.16; 95% CI -0.20, 0.05). Fig. 3 depicts overall task-effects.

3.1.2. fMRI results - task-related activity

To examine main effects in anticipatory task-related activity for the anticipation of restricted breathing, we performed ROI and whole-brain analyses. ROI-based analyses for the contrast of interest '*anticipation > baseline*' revealed significant activations in the bilateral anterior dorsal and in the left anterior ventral insula (small-volume FWE-corrected peak-voxel: $p < .05$; Table 3; Fig. 4). Analyses in the remaining ROIs did not reveal any further significant activation (all FWE-corrected peak-voxel: $p > .05$). Whole-brain analysis revealed additional activations in the calcarine sulcus, in the right posterior insula and in the right TPJ, specifically in the right angular gyrus of the inferior parietal lobule (all whole-brain FWE-corrected peak-voxel: $p < .05$; Table 4). For completeness, tables for the contrasts '*anticipation > restriction*' (activation in anterior and midcingulate cortex) and '*restriction > anticipation*' (activation in anterior dorsal insula) are shown in the supplementary material.

To examine if brain activity during the anticipation of restricted breathing was related to levels of interoceptive prediction, we performed correlational analyses of significant task related peak-voxel activity with the difference score between the rating of the experienced body-state during breathing restriction and the rating of the anticipated body-state of breathing restriction (termed as Δ-dyspnea, Δ-pleasantness and Δ-unpleasantness as experienced - anticipated). Brain-behavior analyses revealed a significant positive correlation of Δ-dyspnea and the slope of signal increase in the left ventral anterior insula during anticipation of the impending breathing restriction ($r = 0.517$, $p < .01$; Fig. 5). Thus, a faster signal increase during anticipation was associated with an 'under-estimation' of the body state (i.e., positive prediction error). Similar associations were observed between the slope of this region and Δ-unpleasantness ($r = 0.445$, $p = .008$; Suppl. Table 5) and Δ-pleasantness ($r = .-363$, $p = .035$; Suppl. Table 5), which did however not survive FDR correction (Table 5). An association was observed between Δ-dyspnea and peak-voxel activity in the left ventral anterior insula ($r = 0.354$, $p = .04$; Table 5 and Suppl. Table 5), which did however not remain significant after global FDR correction (i.e., FDR correction for the amount of peak-voxel activity across ROIs). Activation of the right TPJ during the anticipation of the impending breathing restriction was positively associated with Δ-dyspnea ($r = 0.467$, $p < .01$; Fig. 6). Hence, an 'under-estimation' of the body state (i.e., positive prediction error) was associated with more activation in TPJ. Activation in the visual cortex (i.e., calcarine cortex) was not considered as being relevant for further brain self-report analyses. No other associations were observed ($p > .05$). Table 5 depicts a summary of the results and full correlation tables are shown in the supplementary material (Suppl. Table 5).

3.1.3. fMRI results - functional connectivity

We performed a network-based task-related functional connectivity approach (Fornito et al., 2012; Zalesky et al., 2010) to investigate if we could identify a task induced network configuration (i.e., sub-network) during the anticipation of future aversive interoceptive states that would specifically relate to the level of interoceptive predictions. Using the network-based statistics approach, we observed a significant positive correlation of Δ-dyspnea to functional connectivity in a network spanning 54 regions ($p < .001$, FWE corrected, initial link threshold = 0.05; Fig. 7) including among others the anterior and posterior insula, TPJ and regions of the cognitive control network. Thus, an 'under-estimation' of the body state (i.e., positive prediction error) during the breathing task was associated with stronger connectivity in this subnetwork. Furthermore, we observed a significant negative association of Δ-dyspnea in a network of 33 regions ($p < .001$, FWE-corrected, initial link threshold = 0.005; Fig. 8) not including the insular cortex but including among others regions of the cognitive control network (i.e., preSMA) and TPJ. Here, 'over-estimations' of the body state (i.e., negative prediction error)

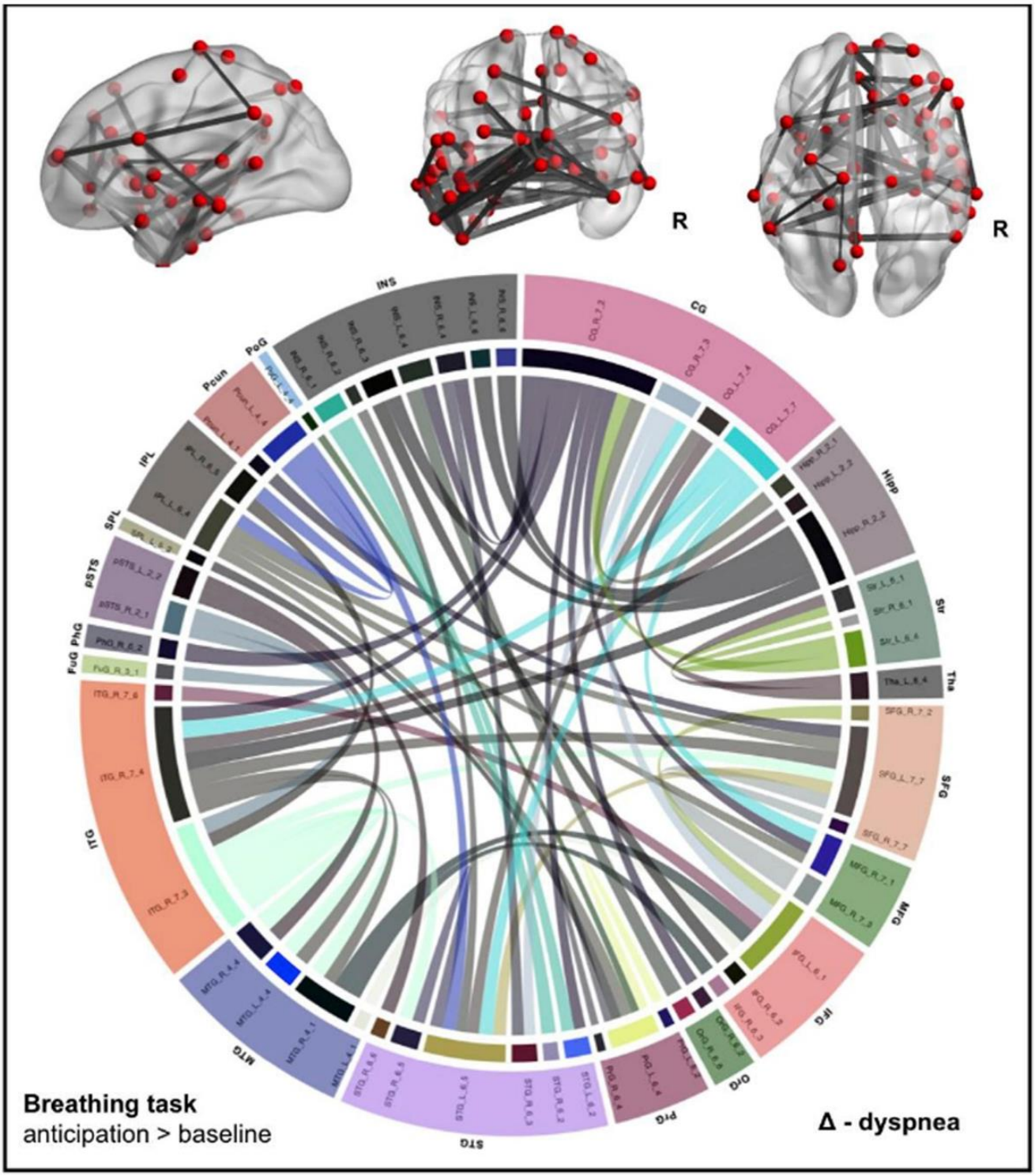

Fig. 7. Using the network-based statistics approach, we observed a significant positive correlation of Δ-dyspnea to functional connectivity in a network spanning 54 regions ($p < .001$, FWE corrected) including among others the anterior and posterior insula, TPJ and regions of the cognitive control network. Thus, an 'under-estimation' of the body state (i.e., positive prediction error) during the breathing task was associated with stronger connectivity in this subnetwork. Line thickness indicates strength of correlation between Δ-dyspnea and connectivity. Abbreviations from Brainnetome atlas (see BNA subregions file in the supplement).

during the breathing task were associated with stronger connectivity in this subnetwork. Comparisons revealed that these 2 networks only overlapped with 5 nodes (left TPJ, right and left superior frontal gyrus, left inferior frontal gyrus, right cingulate gyrus).

3.2. Experiment 2: craving regulation task

3.2.1. Behavioral results - overall task effects

The experimental manipulation of maximizing craving temptation

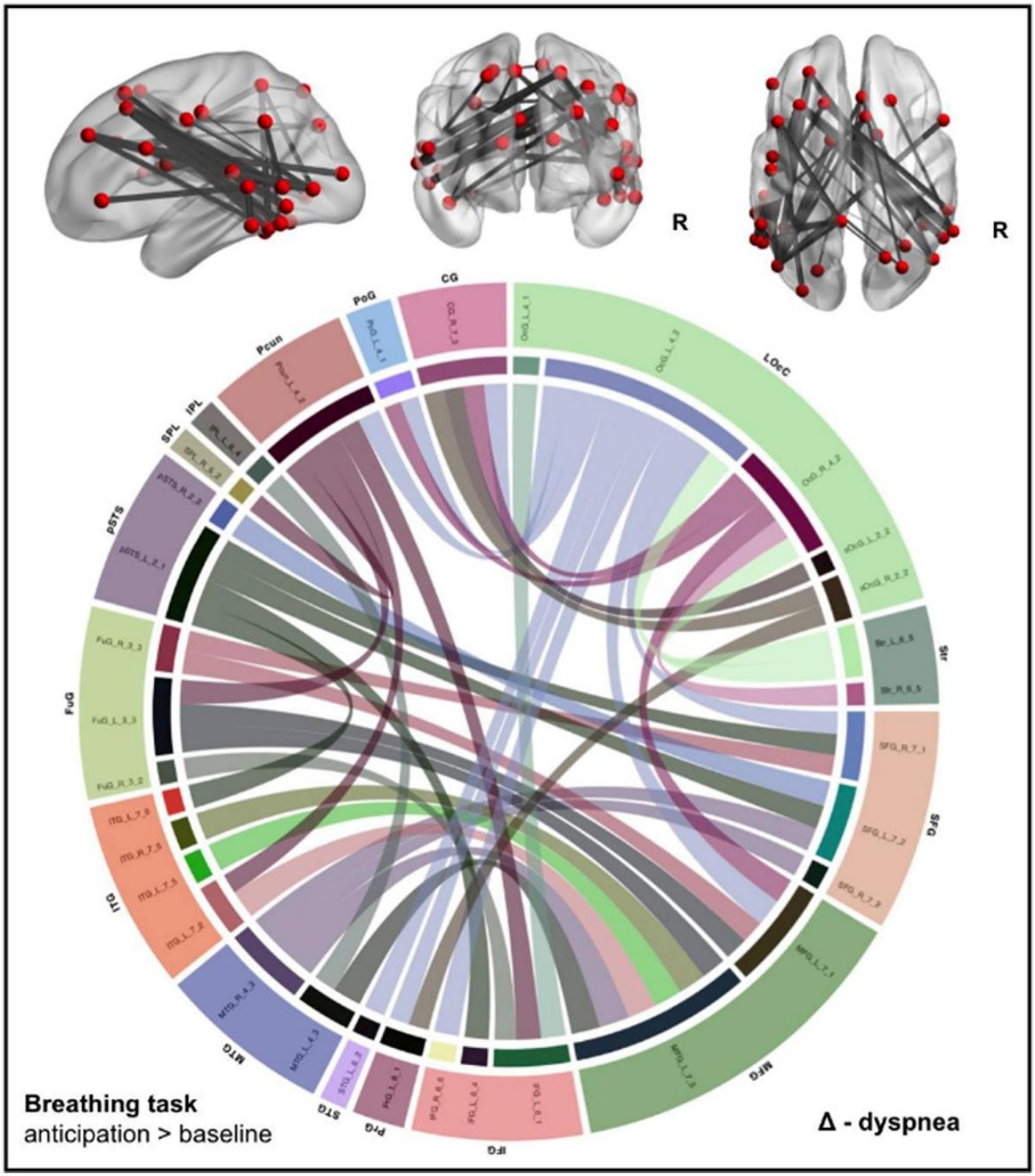

Fig. 8. Using the network-based statistics approach, we observed a significant negative association of Δ-dyspnea in a network of 33 regions ($p < .001$, FWE-corrected) not including the insular cortex but including among others regions of the cognitive control network (i.e., preSMA) and TPJ. Here, 'over-estimations' of the body state (i.e., negative prediction error) during the breathing task were associated with stronger connectivity in this subnetwork. Line thickness indicates strength of correlation between Δ-dyspnea and connectivity. Abbreviations from Brainnetome atlas (see BNA subregions file in the supplement).

induced by the snacks assigned to the self-control-strategy (as rated by the participants prior to the experiment) was successful as we observed significantly higher craving ratings for this condition as compared to the snacks assigned to the control condition (pre-craving ratings: control condition = 2.99; self-control-condition: 3.76; 95% CI: 0.87, −0.67; $p < .05$). During the self-control task, we observed a significant interaction effect of condition*rating dimension with $F(1.14, 43.45) = 42.24$, $p < .001$, Greenhouse-Geisser correction). Specifically, post-hoc paired

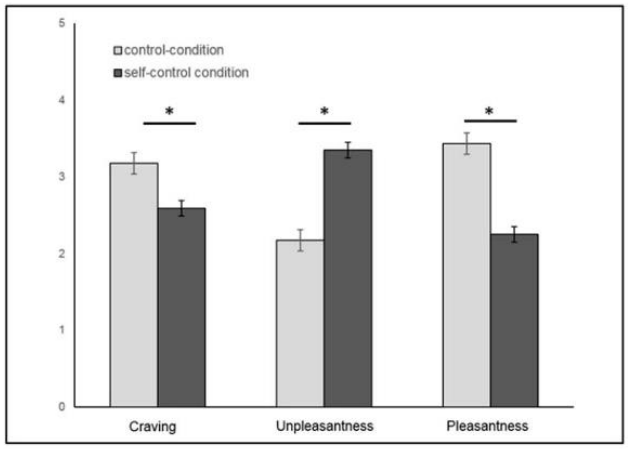

Fig. 9. Overall task-effects in the craving-regulation task (experiment 2). * Post-hoc paired sample t-tests with $p < .001$. Error-bars represent standard error of the mean (see main text for CI's of difference scores).

sample t-tests with the craving ratings obtained during the experiment revealed that the self-control strategy was associated with significantly lower craving ratings than the control condition (control condition = 3.18, SE = 0.16; self-control condition = 2.59, SE = 0.12; 95% CI: 0.29, 0.88; $p < .001$) indicating that craving could be successfully down-regulated. A similar pattern of overall emotional experience could be observed with reduced pleasantness ratings (pleasantness-control: 3.44, SE = 0.14; pleasantness-self-control: 2.26, SE = 0.09; 95% CI: 0.82, 1.54; $p < .001$) and elevated unpleasantness ratings in the self-control as compared to the control condition (unpleasantness-control: 2.18, SE = 0.13; unpleasantness-self-control: 3.35, SE = 0.10; 95% CI: 1.52, −0.82, $p < .001$). Fig. 9 depicts overall task-effects.

3.2.2. *fMRI results - task-related activity*

To examine main effects in brain activity for the down-regulation of craving (i.e., self-control), we performed ROI and whole-brain analyses. ROI-based analyses for the contrast of interest '*self-control > control-condition*' revealed significant activations in the bilateral anterior dorsal insula (small-volume FWE-corrected peak-voxel: $p < .05$; Table 6; Fig. 10), the vlPFC (small-volume FWE-corrected peak-voxel: $p < .05$; Table 6; Fig. 10) and the bilateral preSMA (small-volume FWE-corrected peak-voxel: $p < .05$; Table 6; Fig. 10). Analyses in the remaining ROIs did not reveal any further significant activation (all FWE-corrected peak-voxel: $p > .05$). Whole-brain analysis only revealed significant activation in the vlPFC which has been identified already by the ROI-analyses (whole-brain FWE-corrected peak-voxel: $p < .05$). For completeness, results for the contrast '*control-condition > self-control*' are shown in the supplementary material. Of note, when correcting for multiple comparisons (FDR) with the number of peak-voxels across ROIs, activations in the anterior dorsal insula and the left peak-voxel within the preSMA did not remain significant (Table 7).

To examine if brain activity during the down-regulation of craving was related to levels of self-control or affective regulation, we performed correlational analyses of significant task related peak-voxel activity with the difference score between the self-control condition and the control condition (termed as Δ-craving, Δ-pleasantness, Δ-unpleasantness; control condition > self-control). We observed a significant positive correlation of Δ-craving and activation of the left preSMA during downregulation of craving via negative future thinking strategies ($r = 0.348$, $p < .05$; Fig. 11; Table 7). Thus, higher levels of self-control success during the down-regulation of craving were associated with higher levels of activation in left preSMA (this association did not remain significant after FDR correction). Similarly, we observed significant associations of activity in the preSMA to Δ-unpleasantness (left: $r = -0.529$, $p < .01$; right: $r = -0.588$, $p < .001$; Fig. 12 A + B) and Δ-pleasantness (left: $r = 0.596$, $p < .001$; right: $r = 0.455$, $p < .01$; Fig. 12 C + D). No other associations to any of the neural activity was observed ($p > .05$). Table 7 depicts a summary of the results and full correlation tables are shown in the supplementary material (Suppl. Table 7).

3.2.3. *fMRI results - functional connectivity*

To examine if we could identify a task induced network configuration (i.e., sub-network) during the down-regulation of craving to palatable foods via negative future thinking strategies that would specifically relate to the level of self-control success (i.e., the amount of regulated craving; Δ-craving), we performed network-based task-related functional connectivity analyses with the contrast '*self-control condition > control condition*' as the contrast of interest. Network-based statistics analyses revealed a significant positive correlation of Δ-craving to connectivity in a network of 132 regions ($p < .001$, FWE corrected, initial link threshold = 0.005; Fig. 13) including among others the cognitive control network, TPJ and insula. Thus, higher levels of self-control success during the downregulation of craving were associated with stronger connectivity in this global network. By increasing the initial-link threshold, this large network could be broken down into two subnetworks with highest effect size. One of these networks included 11 regions among others the insula and TPJ ($p < .001$, FWE corrected, initial link threshold = 0.001; Suppl. Figure 1), whereas the other network was comprised of 13 regions including among others orbitofrontal and inferior temporal regions ($p < .001$, FWE corrected, initial link threshold = 0.001; Suppl. Figure 2).

3.3. *Behavioral association of self-control and interoceptive prediction*

In order to replicate that levels of self-control would be associated with the degree to which an individual maintains predictive models of his or her own interoceptive state, we performed a partial correlation analysis along

Table 6
Results of experiment 2: ROI analyses with voxel-wise one-sample *t*-test for the contrast 'self-control > control condition' (n = 39).

ROI number	ROI name	Cluster size	Peak-voxel activity			*p* – peak voxel FWE	FDR corrected *p* for the number of peak-voxel (i.e., 11 across ROIs)
			x	y	z		
1	anterior ventral insula L	–	–	–	–	1*	1
2	anterior ventral insula R	–	–	–	–	1*	1
3	anterior dorsal insula L	2	−37	24	2	0.049	0.089
4	anterior dorsal insula R	5	42	14	−3	0.038	0.089
5	midcingulate cortex LR	–	–	–	–	1*	1
6	ventrolateral PFC LR	206	−39	28	−1	<0.001	0.0061
		68	−57	26	20	0.017	0.0628
7	dorsolateral PFC LR	20	−39	28	24	0.051	0.089
8	preSMA LR	353	−9	6	60	<0.001	0.0061
		51	8	8	68	0.037	0.089
9	temporoparietal junction LR	–	–	–	–	1*	1

FWE: family wise error corrected; FDR: false discovery rate; PFC = prefrontal Cortex; SMA = supplementary motor area; * a probability of 1 was assigned to ROIs without supra-threshold voxels for inclusion into FDR adjustments.

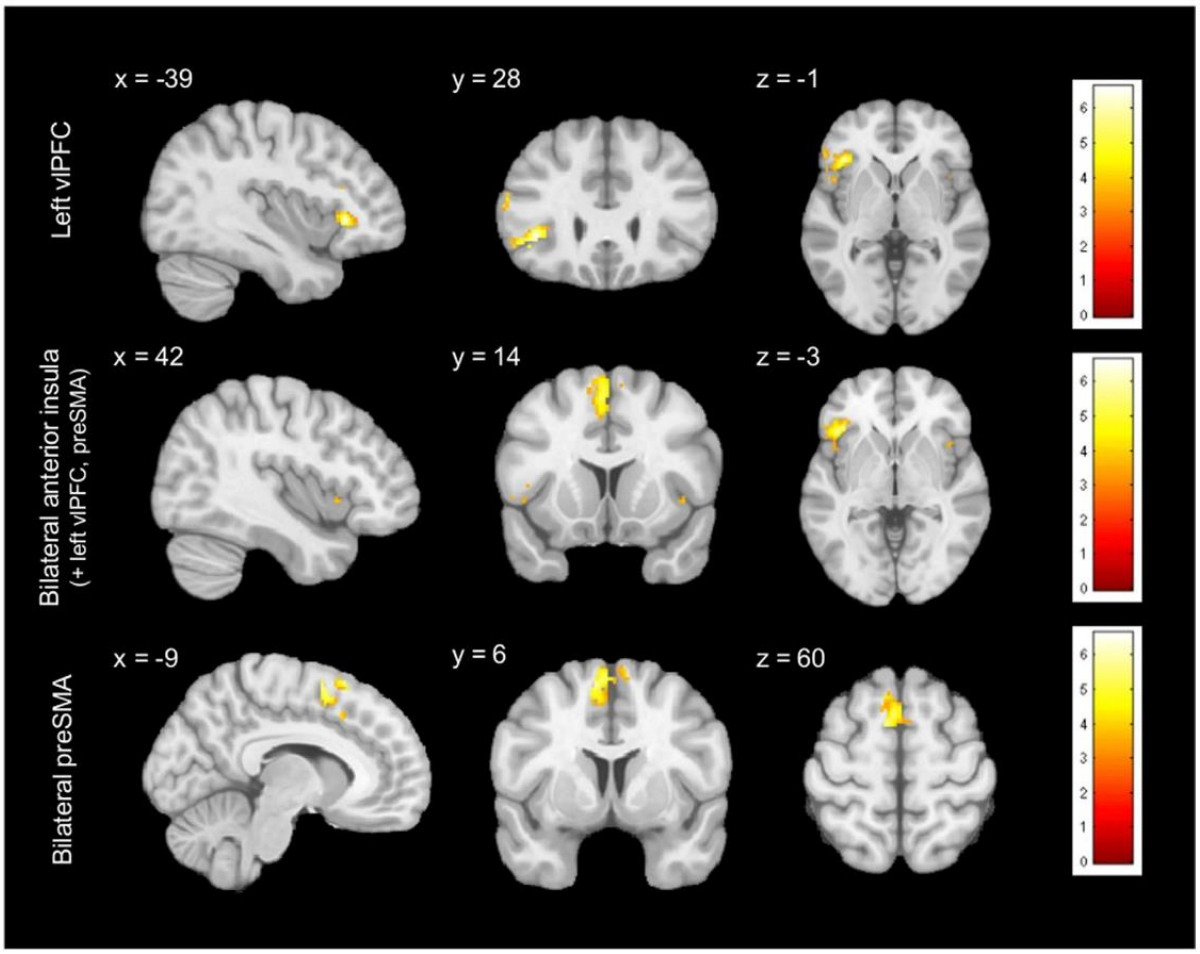

Fig. 10. Main effects in the craving-regulation task - ROI-based analyses for the contrast of interest '*self-control* > *control-condition*' revealed significant activations in the vlPFC (small-volume FWE-corrected peak-voxel: $p < .05$; Table 6), the bilateral preSMA (small-volume FWE-corrected peak-voxel: $p < .05$; Table 6), and the bilateral anterior dorsal insula (small-volume FWE-corrected peak-voxel: $p < .05$; Table 6). Activity in the insula and the left preSMA did not remain significant after global FDR correction with the number of peak-voxel across ROIs. Whole-brain analysis only revealed significant activation in the vlPFC, which has been identified already by the ROI-analyses (whole-brain FWE-corrected peak-voxel: $p < .05$).

the dimension of sensory experience (i.e., 'what is sensed'). This analysis revealed a significant association ($r = -0.344$, $p < .05$, one-tailed testing; Fig. 14 A) between the amount of self-control success (i.e., Δ-craving as the difference of craving ratings between the self-control condition and the control condition; control condition > self-control) and level of interoceptive prediction (i.e., Δ-dyspnea as the difference of the perceived dyspnea and anticipated dyspnea; experienced > anticipated). This association revealed that individuals who predicted elevated interoceptive states with respect to dyspnea intensity than actually experienced (i.e.,"over-estimated" their interoceptive state; negative prediction error) were more effective in the down-regulation of craving. No significant association was observed for |Δ|-dyspnea (i.e., the absolute difference scores) when performing post-hoc correlational analyses. Furthermore, we observed a significant association between the level of interoceptive prediction (Δ-dyspnea) and scores of the Self-Regulation Scale ($r = -0.291$, $p < .05$, one-tailed testing; Fig. 14 B). Additional analyses in the affective dimension again did not reveal any significant associations between the amount of emotions elicited during self-control and level of emotional interoceptive prediction (association of Δ-unpleasantness craving regulation and Δ-unpleasantness breathing restriction: $r = -0.113$, $p > .05$; association of Δ-pleasantness craving regulation and Δ-pleasantness breathing restriction: $r = 0.023$, $p > .05$). Post-hoc correlational analyses with the absolute rating values and not the difference scores of anticipated/experienced dyspnea and craving did not reveal any significant associations (all $p > .05$).

Cross-categorical correlational analyses between all difference measures (i.e., Δ) derived from both experiments (independent of 'what is sensed' and 'how it feels'), did not reveal any other significant associations when correcting for multiple comparisons. However, without correction for multiple comparisons, we observed a trend towards associations of Δ-dyspnea to all measures acquired in the self-control task (i.e., Δ-craving, Δ-unpleasantness, Δ-pleasantness). None of the measures underlying the affective dimension in breathing restriction task showed an association to the self-control task. Table 8 depicts these cross-categorical correlational results.

3.4. Brain behavior relationship across tasks

3.4.1. Brain behavior - task-related activity

(1) is the level of anticipatory brain activity in response to an aversive interoceptive state (breathing task - fMRI) associated with level of self-control success (craving regulation task - behavior)?

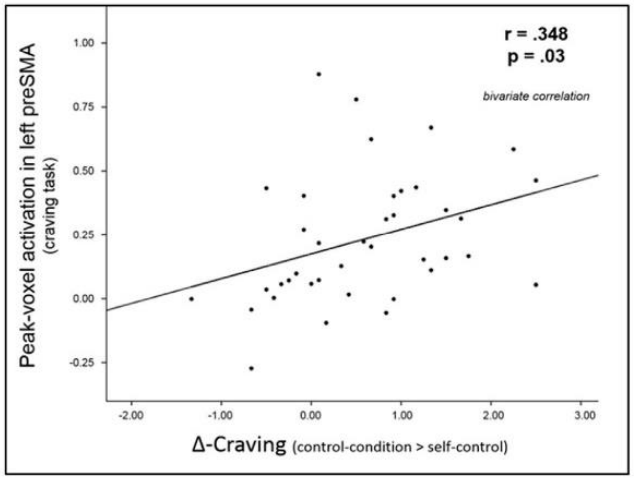

Fig. 11. In the craving regulation task (experiment 2) we observed a significant positive correlation between amount of self-control success (i.e., Δ-craving as the difference of craving ratings between the control condition and self-control condition) and peak-voxel activation of the left preSMA (preSMA = pre-supplementary motor area). Thus, higher levels of self-control success during the down-regulation of craving were associated with higher levels of activation in left preSMA. Of note, this association did not remain significant after FDR corrections (c.f., Table 7).

Brain-behavior analyses between tasks revealed a significant negative correlation between the peak-voxel activation of the bilateral dorsal anterior insula during the anticipation of breathing restriction and Δ-craving (left: $r = -0.376$, $p < .05$; right: $r = -0.370$, $p < .05$; Fig. 15 AB). Thus, those subjects that showed the greatest activation in the dorsal anterior insula when anticipating an aversive state also showed the lowest levels of self-control during the craving task (this association did not remain significant when FDR correction was applied for the total number of between task correlations; c.f., Table 5). Analyses with the signal slopes of the insula during anticipation of the breathing load and Δ-craving did not reveal any significant associations. Whole-brain significant peak-voxel activity of the TPJ was also not correlated with Δ-craving ($p > .05$). Activation in the visual cortex (i.e., calcarine cortex) was not considered as being relevant for further brain self-report analyses. Table 5 depicts a summary of the results and full correlation tables are shown in the supplementary material (Suppl. Table 8).

(2) is the level of brain activity during down-regulation of craving (craving task - fMRI) associated with levels of interoceptive prediction (breathing task - behavior)?

Conversely, analyses revealed a significant negative correlation of activation of the right preSMA during the down-regulation of craving and Δ-dyspnea ($r = -0.461$, $p < .01$; Fig. 16). Thus, those subjects with a more accurate interoceptive prediction or those who 'over-estimated' their body state (i.e., 'negative prediction error') during the breathing task also showed greater activation in preSMA during the down-regulation of craving as compared to individuals who 'under-estimated' the interoceptive state. Of note, this association did not remain significant when correction for multiple comparisons was applied (FDR-correction with 12 comparisons; Table 7). Activity in the vlPFC was not significantly associated with Δ-dyspnea. Table 7 depicts a summary of the results and full correlation tables are shown in the supplementary material (Suppl. Table 9).

3.4.2. Brain behavior - functional connectivity

(1) is there a subnetwork during the anticipation of the aversive interoceptive state (breathing task - fMRI) that is associated with levels of self-control success (craving regulation task - behavior)?

Network-based statistics revealed a network of 70 regions in which the connectivity was significantly positive correlated to Δ-craving during the anticipation of the breathing load ($p < .001$, FWE-corrected, initial link threshold = 0.0025; Fig. 17). This network included among others the insula, the TPJ and regions of the cognitive control network (incl. preSMA). Thus, those subjects with the greatest levels of connectivity in this subnetwork during the anticipation of the aversive interoceptive state showed also the highest levels of self-controlled behavior in the craving task.

(2) is there a subnetwork during the down-regulation of craving (craving task - fMRI) that is associated to levels of interoceptive prediction (breathing task - behavior)?

Vice versa, we observed a network of 82 regions in which the connectivity was significantly negative correlated to Δ-dyspnea during the down-regulation of craving ($p < .001$, FWE-corrected, initial link threshold = 0.01; Fig. 18). This network included among others the insula, the TPJ and regions of the cognitive control network. Hence, those subjects with the greater levels of connectivity in this subnetwork during the down-regulation of craving 'over-estimated' their body state (i.e., negative prediction error) during the breathing task.

4. Discussion

Following the interoceptive inference framework, we set out to replicate our previously reported association of self-control and interoceptive prediction (Kruschwitz et al., 2019). Moreover, we strived to investigate the neural underpinnings subserving the relationship between self-control and aversive interoceptive predictive models. To this end, we used fMRI and a within-subject design including an inspiratory breathing-load task to examine the prediction of aversive interoceptive perturbation and a craving-regulation for tasty snacks task to measure self-control. In this current study, we could successfully replicate previous effects with an independent sample as we observed that individuals who 'over-estimated' their upcoming interoceptive state with respect to experienced dyspnea (i.e., anticipated versus experienced) were more effective in the down-regulation of craving using negative future-thinking strategies. These individuals, again, obtained higher scores on a measure of trait self-control, i.e. self-regulation to achieve long-term goals. On a neural level, we found evidence that the anterior insula (AI; interoceptive processing; Craig, 2003; Seth, 2015) and the presupplementary motor area (preSMA; self-regulation; Nachev et al., 2008, Tabibnia et al., 2014; Han et al., 2018; Langner et al., 2018), which were recruited in both tasks (*breathing restriction task*: AI activity, AI and preSMA connectivity; *craving task*: AI and preSMA activity, AI connectivity), partly accounted for these effects. Specifically, levels of AI activation during the anticipation of the aversive interoceptive state (breathing restriction) were associated with self-controlled behavior in the craving task, whereas levels of interoceptive prediction during the breathing task were conversely associated with activation in preSMA during the down-regulation of craving, whose anticipatory activity was correlated with self-control success (see Fig. 19 for a summary). Moreover, during the self-control task, levels of interoceptive prediction were associated with connectivity in a spatially distributed network including among other areas the insula and regions of cognitive control, while during the interoceptive prediction task, levels of self-control were

Table 7
Results summary of the applied analysis scheme for the layer of task activity in experiment 2 (craving task) and the associated between-task brain-behavior correlational analysis (c.f. *results* section 3.4).

		Within-task activity (Table 5)			Within task brain-behavior correlation for craving (Suppl. Table 7)			Within task brain-behavior correlation for pleasantness and unpleasantness (Suppl. Table 7)		Between-task correlation with either dyspnea or craving (Suppl. Table 9 and Fig. 19)	
	Brain region	Exploratory p (within ROI peak-voxel FWE-correction)	FDR corrected p for the number of peak-voxel (11 across ROIs) or whole-brain FWE corrected p	Insula slope extraction (ROI average) if insula survived FDR correction	Correlation targets (3 in total)	Exploratory p (uncorrected)	FDR corrected p (3 comparisons)	Exploratory p (uncorrected)	FDR corrected p (6 comparisons)	Exploratory p (uncorrected)	FDR corrected p (12 comparisons: 9 breathing plus 3 craving)
ROI	anterior ventral insula L	n.s.	n.s.	–	–	–	–	–	–	–	–
	anterior ventral insula R	n.s.	n.s.	–	–	–	–	–	–	–	–
	anterior dorsal insula L	☑ p = .049	n.s.	–	–	–	–	–	–	–	–
	anterior dorsal insula R	☑ p = .038	n.s.	–	–	–	–	–	–	–	–
	midcingulate cortex LR	n.s.	n.s.		–	–	–	–	–	–	–
	ventrolateral PFC LR (first peak)	☑ p < .001	☑ p = .006		peak	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	ventrolateral PFC LR (second peak)	☑ p = .017	n.s.		–	–	–	–	–	–	–
	dorsolateral PFC LR	n.s.	n.s.		–	–	–	–	–	–	–
	preSMA LR (first peak L)	☑ p < .001	☑ p = .006		peak	☑ craving p = .03	n.s.	☑ unpleasantness: p = .001; pleasantness: p < .001	☑ unpleasantness: p = .002 pleasantness: p = .002	n.s.	n.s.
	preSMA LR (second peak R)	☑ p = .037	n.s.		peak*	n.s.	n.s.	☑ unpleasantness: p < .001; pleasantness: p = .004	☑ unpleasantness: p = .002 pleasantness: p = .006	☑ dyspnea p = .006	n.s.
	temporoparietal junction LR	n.s.	n.s.		–	–	–	–	–	–	–

FWE: family wise error corrected; FDR: false discovery rate; SMA = supplementary motor area; PFC = prefrontal cortex; *although not significant after FDR correction, brain self-report analyses were conducted due to the seemingly bilateral nature of effects within the same ROI.

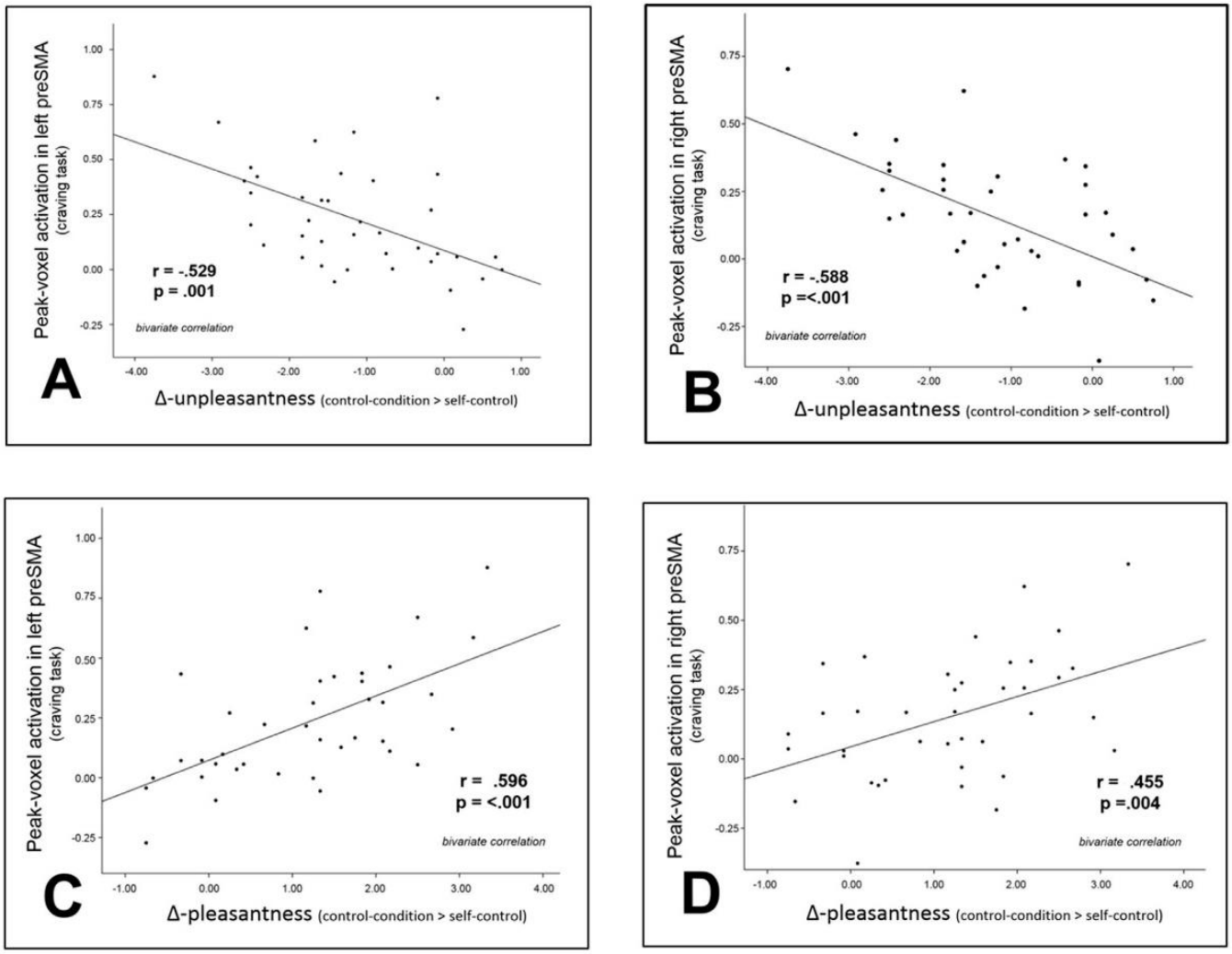

Fig. 12. In the craving regulation task (experiment 2) we observed a significant negative correlation between the difference of unpleasantness ratings between the control condition and self-control condition and the peak-voxel activation of the bilateral preSMA (A + B) and a significant positive correlation between the difference of pleasantness ratings and the peak-voxel activation of the bilateral preSMA (C + D) (preSMA = pre-supplementary motor area). Thus, higher levels of affective regulation during the down-regulation of craving were associated with higher levels of activation in bilateral preSMA.

associated with connectivity in a spatially distributed network including among other regions the insula and preSMA. Taken together, these findings consolidate the notion that self-control is directly linked to interoceptive inference and highlight the contribution of AI and preSMA as potential candidate regions underlying this relationship. Therefore, the AI and preSMA could be treatment targets for interventions aimed at improving self-control in situations referring to the prediction of future internal states.

To avoid events that might counteract homeostasis, our brain permanently anticipates future states of our body (Barrett and Simmons, 2015; Seth and Friston, 2016). Discrepancies between 'top-down' predictions generated by the brain and incoming sensory signals may foreshadow such events. To confirm the perceptual predictions, actions can be initiated to decrease the interoceptive prediction error via active inference (Gu and FitzGerald, 2014; Seth and Friston, 2016). From this it follows, that 'top-down' predictions of future interoceptive states can strongly influence our actions, which are therefore not only a function of the current homeostatic state. That is, if predicted interoceptive models diverge from actual experience, choices may result that lead to outcomes not necessarily consistent with our long-term goals, for example failures in self-control (Kruschwitz et al., 2019). Consistent with these assumptions and with our previous study, we observed that individuals who 'over-estimated' the future aversive state obtained higher levels of self-control when asked to down-regulate their craving to snacks by application of future-thinking strategies. Importantly, in our previous study we were not able to make conclusions about the direction of observed effects in terms of directed (i.e., positive and negative) interoceptive prediction errors or absolute prediction errors ($|\Delta|$) because we previously observed effects for both, Δ and $|\Delta|$. However, in this current study we only observed effects for Δ (dyspnea: experienced > anticipated), which is more consistent with the assumption that our body needs to avoid harmful events to effectively satisfy physiological needs. That is, a non-pathological 'over-estimation' of an aversive interoceptive state may effectively lead to avoidance of situations that might counteract homeostasis. Furthermore, this observation stays in line with recent ideas of active inference in interoceptive psychopathology (Paulus et al., 2019) suggesting the existence of directed prediction errors. Specifically, it was proposed that interoceptive psychopathology partly arises from abnormally strong expectations of situations that elicit bodily change (i.e., hyperprecise priors). For example, in patients with anorexia nervosa (AN) it was shown that they experienced cardiorespiratory visceral illusions (i.e., presence of interoceptive sensation without visceral change) in the premeal state, a time period known to trigger strong feelings of anxiety and fear in AN patients (Khalsa et al., 2015).

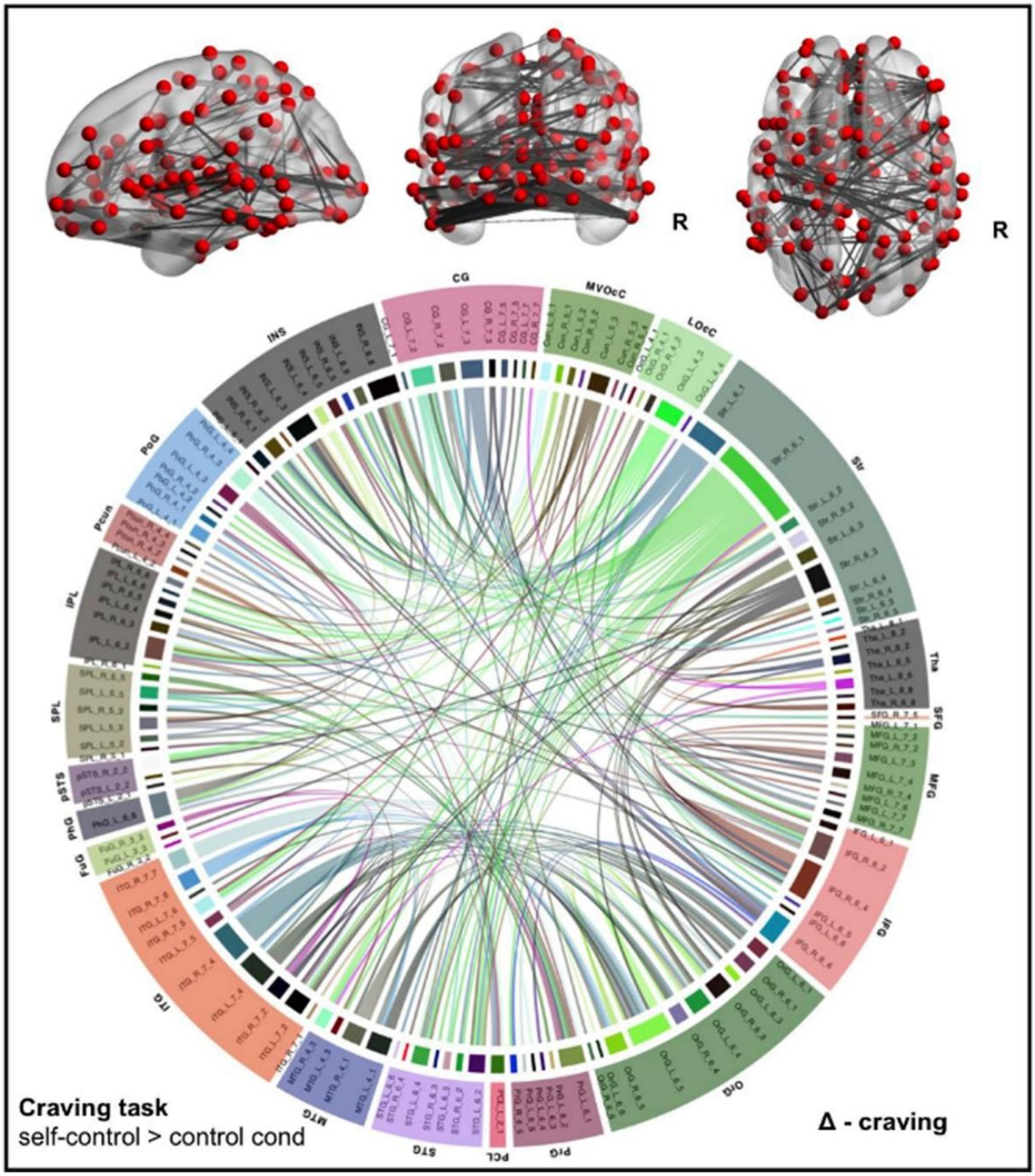

Fig. 13. Network-based statistics analyses revealed a significant positive correlation of Δ-craving to connectivity in a network of 132 regions ($p < .001$, FWE corrected) including among others the cognitive control network, TPJ and insula. Thus, higher levels of self-control success during the downregulation of craving were associated with stronger connectivity in this global network. This large network could be broken down into two subnetworks with highest effect size (Suppl. Fig. 1 and 2). Line thickness indicates strength of correlation between Δ-craving and connectivity. Abbreviations from Brainnetome atlas (see BNA subregions file in the supplement).

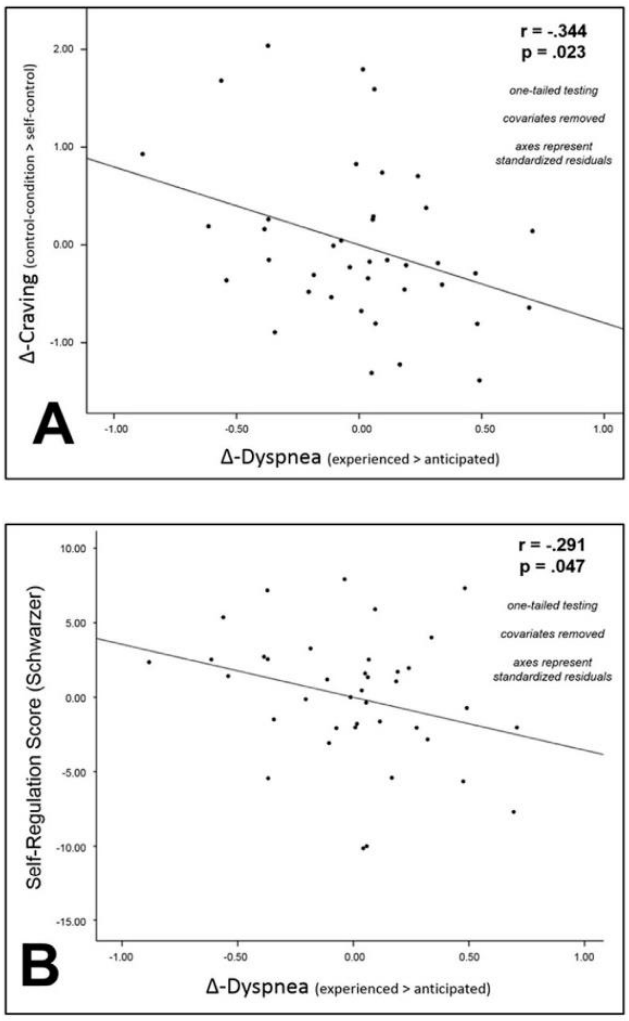

Fig. 14. In the behavioral analysis across tasks we observed a significant association between level of interoceptive prediction as measured in the inspiratory breathing restriction task (i.e., Δ-dyspnea) and two distinct measures of self-control success: (A) significant correlation with the amount of self-control success as measured the craving regulation task (i.e., Δ-craving) and (B) significant correlation with the Self-Regulation Scale (n = 39, partial regression residual plot, one-tailed testing due to expected direction of effects, covariates removed). Thus, individuals who predicted elevated interoceptive states with respect to dyspnea intensity than actually experienced (i.e.,"over-estimated" their interoceptive state; negative prediction error) were more effective in the down-regulation of craving and also obtained higher scores on a measure of trait self-control.

From this it was speculated that hyperprecise priors may lead to elevated self-controlled behavior in the context of food related choices. In line with the assumed role of a prediction error in active inference (i.e., the difference between 'top-down' predictions and incoming sensory signals) and similar to our previous study, we did not observe significant associations between scores of the self-control task and rating values of 'anticipated' and 'experienced' body state in the breathing restriction task but only found this for their difference scores, i.e. interoceptive prediction error.

Although this is only the second study demonstrating a direct association of self-controlled behavior and interoceptive prediction, links between interoceptive awareness and self-control have been provided by previous studies. In line with the somatic marker hypothesis (Damasio, 1996), it was demonstrated that the relationship between the processing

Table 8
Cross-categorical (partial) correlation analyses between all difference measures (i.e., Δ) derived from both experiments. Covariates were the breathing baseline measures (respectively), physical exercise scores, and age. In the craving regulation task, differences are computed as 'control condition > self-control', whereas differences in the breathing restriction task are computed as 'experienced > anticipated'. As a secondary measure for the breathing task, we computed the absolute values of the difference scores |Δ| because simple Δ resulted in negative values for some individuals. *one-tailed testing as the direction of the effect was given by the previous behavioral study (c.f., Kruschwitz et al., 2019).

Breathing restriction task	Craving regulation task		
	Δ-craving	*Δ-unpleasantness*	*Δ-pleasantness*
Δ-dyspnea	r = **-.344, p = .023***	r = .327, p = .059	r = −.338, p = .051
Δ-unpleasantness	r = −.151, p > .05	r = −.113, p > .05	r = −.003, p > .05
Δ-pleasantness	r = .085, p > .05	r = .102, p > .05	r = .023, p > .05
|Δ|-dyspnea	r = −.205, p > .05	r = .302, p > .05	r = −.266, p > .05
|Δ|-unpleasantness	r = −.132, p > .05	r = .186, p > .05	r = −.186, p > .05
|Δ|-pleasantness	r = −.122, p > .05	r = .188, p > .05	r = −.252, p > .05

of bodily signals (Dunn et al., 2010) or AI activity (Werner et al., 2013) and intuitive decision-making is moderated by interoceptive accuracy. Other studies pointed towards deficits of interoceptive processing in individuals eating in response to emotions (Geliebter and Aversa, 2003) and showed that these individuals exhibit altered interoceptive accuracy (Young et al., 2017) and an increased activity in cognitive control regions and the insula during food-related go/no-go tasks (Wood et al., 2016). With focus on cognitive reappraisal (i.e., a crucial aspect of self-control used to resist immediate temptations), it was demonstrated that interoceptive awareness facilitated down-regulation of affective responses to aversive pictures (Füstos et al., 2013). Indirect links to an association of interoceptive prediction and self-controlled behavior were provided in other studies demonstrating that loss aversion, alexithmia, and high trait anxiety are related to both, an altered perception of bodily signals and different choice behavior (Miu et al., 2008; Sokol-Hessner et al., 2015; Scarpazza et al., 2017). In the clinical context, studies from independent research fields showed that eating disorders, depression and anxiety disorders are associated with interoceptive deficits (Furman et al., 2013; Herbert and Pollatos, 2014; Jenkinson et al., 2018; Quadt et al., 2018), while another study, in turn, depicted that depression and obesity are linked to reduced delay discounting, an important aspect of self-controlled behavior (Privitera et al., 2015). In the context of addiction, it was demonstrated that drug-dependent individuals could be characterized by altered insular response pattern when anticipating or experiencing aversive interoceptive stimuli also during decision-making (Steward et al., 2014, 2015a; 2015b). Based on these reviewed studies it appears that interoceptive awareness seems to provide a common ground for various aspects of self-control and that its corresponding neural substrates may create processing advantages in self-control contexts referring to the prediction of future internal states.

To assess the neural substrates underlying the relationship between self-control and aversive interoceptive predictive models, we performed the previously established inspiratory breathing-load task and the craving-regulation for palatable food task in an fMRI environment. In both tasks, we observed task main effects in brain areas previously described during the processing of the respective task. Specifically, in the craving task, we observed activity related to the down-regulation of craving via future thinking strategies in the AI (only exploratory, c.f., Table 7), preSMA, and ventrolateral prefrontal cortex (c.f., Kruschwitz et al., 2018b; Han et al., 2018; Langner et al., 2018). In the context of craving regulation, the insula has been suggested to encode a future

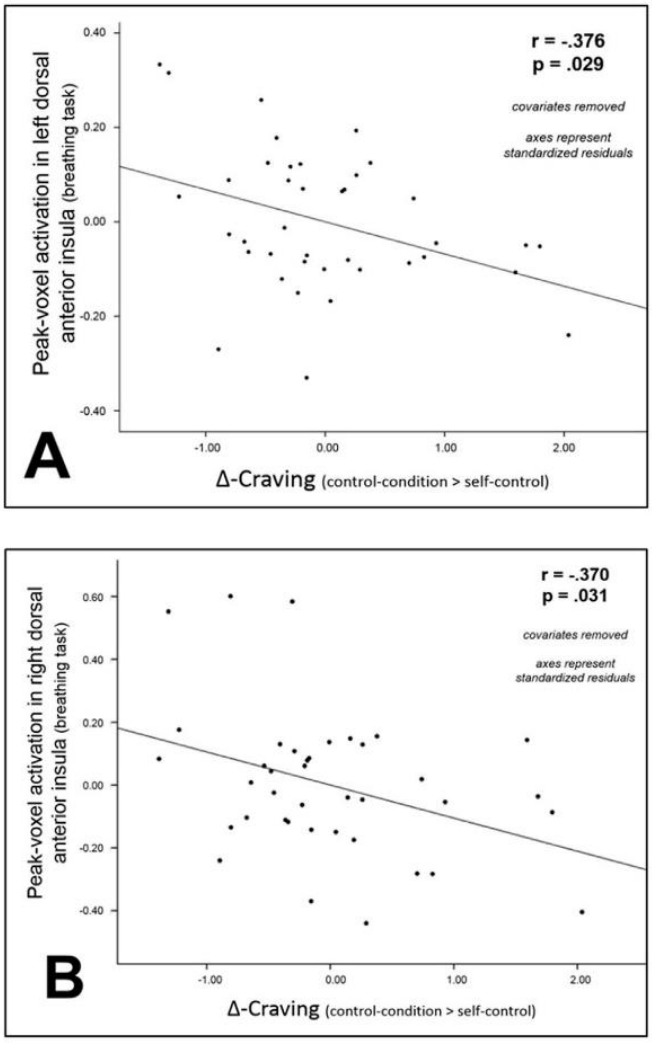

Fig. 15. Across tasks we observed a significant association between amount of self-control success as measured the craving regulation task (i.e., Δ-craving as the difference of craving ratings between the control condition and self-control condition) and peak-voxel activation in left (A) and right (B) dorsal anterior insula as measured in the inspiratory breathing restriction task (n = 39, partial regression residual plot, covariates removed). Thus, higher levels of insula activation during the anticipation of the aversive interoceptive state were hence associated with lower levels of self-controlled behavior in the craving task. Of note, this association did not remain significant when correction for multiple comparisons was applied (FDR-correction with 12 comparisons; Table 5).

bodily state induced by future thinking (Kruschwitz et al., 2018b) and was also discussed as a critical area for translation of interoceptive information to action plans during tasks that require overriding temptations and food craving (He et al., 2014; Han et al., 2018). We also observed a direct brain-behavior relationship between Δ-craving and activation of the left preSMA, indicating that higher levels of self-control success were associated with elevated levels of anticipatory activity in this area. Of note, this relationship did not remain significant when correcting for multiple comparisons (c.f., Table 7). Similarly, we observed significant associations of activity in the preSMA to Δ-pleasantness and Δ-unpleasantness. This brain-behavior relationship closely ties with the preSMAs role as a key region in the self-regulation system processing both, behavioral and emotional control (Kohn et al., 2014; Langner et al., 2018). Moreover, we could identify a large network of 132 regions including, among other areas, regions of the cognitive control network, the insula, and right temporoparietal junction (TPJ)

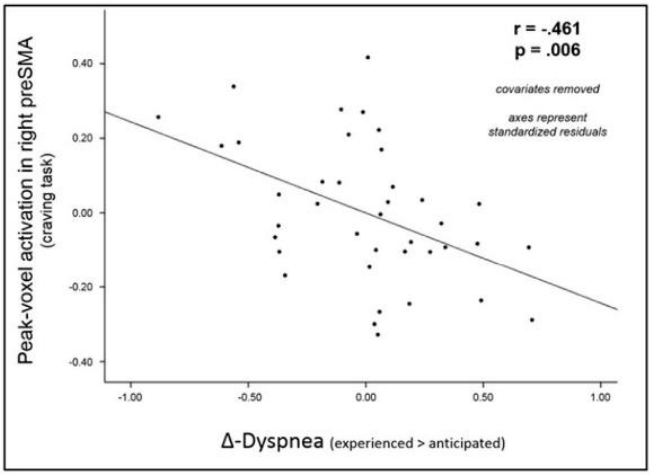

Fig. 16. Across tasks we observed a significant association between level of interoceptive prediction as measured in the inspiratory breathing restriction task (i.e., Δ-dyspnea as the difference of perceived dyspnea and anticipated dyspnea) and peak-voxel activation in right pre SMA as measured in the craving regulation task indicating that those subjects who 'over-estimated' their body state (i.e., 'negative prediction error') during the breathing task also showed greater activation in preSMA during the down-regulation of craving as compared to individuals who 'under-estimated' the interoceptive state (n = 39, partial regression residual plot, covariates removed; preSMA = presupplementary motor area). Of note, this association did not remain significant when correction for multiple comparisons was applied (FDR-correction with 12 comparisons; Table 7).

demonstrating increased connectivity with higher levels of self-control success. Recent meta-analytic evidence pointed towards the role of the right TPJ as another key region in the self-regulation network facilitating emotional regulation and domain-specific self-control of food craving (Han et al., 2018; Langner et al., 2018).

In the breathing task we observed AI activity in response to anticipating the impending breathing load (c.f., Paulus et al., 2012; Haase et al., 2015; Berner et al., 2018), as well as anticipatory activity in the posterior insula and the right TPJ. Substantiating its role for behavioral relevance during the processing of the task, we observed a significant positive correlation of Δ-dyspnea and the slope of signal increase in the ventral AI during anticipation of the impending breathing restriction, indicating that a faster signal increase during anticipation was associated with an 'under-estimation' of the upcoming interoceptive state. This observation ties with recent suggestions that the ventral (and not the dorsal) insula promotes the processing of subjective feeling states (Wager and Barrett, 2017), which in turn were hypothesized to result from interoceptive inference (Seth, 2013). Moreover, lower levels of interoceptive prediction were also associated with more activation in the TPJ. Consistent with the direction of effects in the insula, Berner et al. (2018) showed that recovered AN patients (who can conversely be characterized by hyperprecise priors and 'over-prediction' as compared to an 'under--estimation' of the interoceptive state) obtained hypoactivation of the insula during anticipation of an aversive breathing load. Closely tying with this previous finding, we observed that individuals with higher levels of interoceptive predictions (anticipation > experience) respectively engaged the insula less strongly in a network together with TPJ and cognitive control regions during the anticipation of the load, while rather recruiting other parts of the self-regulation network that consisted of preSMA and TPJ (and others) but not the insula.

Over and above the context of inspiratory breathing restriction and craving regulation, the AI has been considered as the core region of interoceptive prediction (Seth, 2015) and can be regarded as a hub region integrating predictive interoceptive information, as well as affective and cognitive information from other brain regions (Chang et al., 2013;

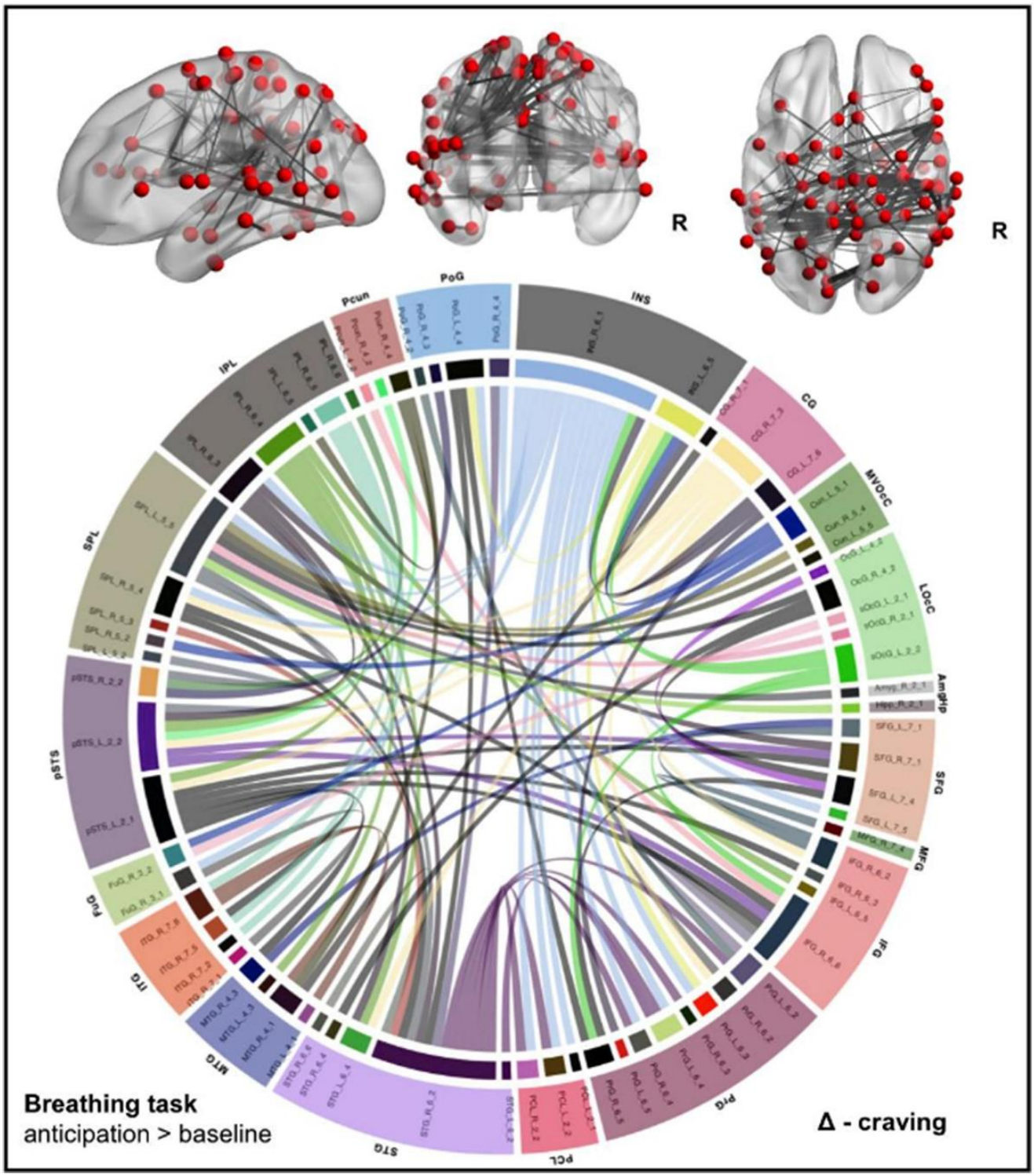

Fig. 17. Network-based statistics revealed a network of 70 regions in which the connectivity was significantly positive correlated to Δ-craving during the anticipation of the breathing load ($p < .001$, FWE-corrected). This network included among others the insula, the TPJ and regions of the cognitive control network (incl. preSMA). Thus, higher levels of connectivity in this subnetwork during the anticipation of the aversive interoceptive state were associated with higher levels of self-controlled behavior in the craving task. Line thickness indicates strength of correlation between Δ-craving and connectivity. Abbreviations from Brainnetome atlas (see BNA subregions file in the supplement).

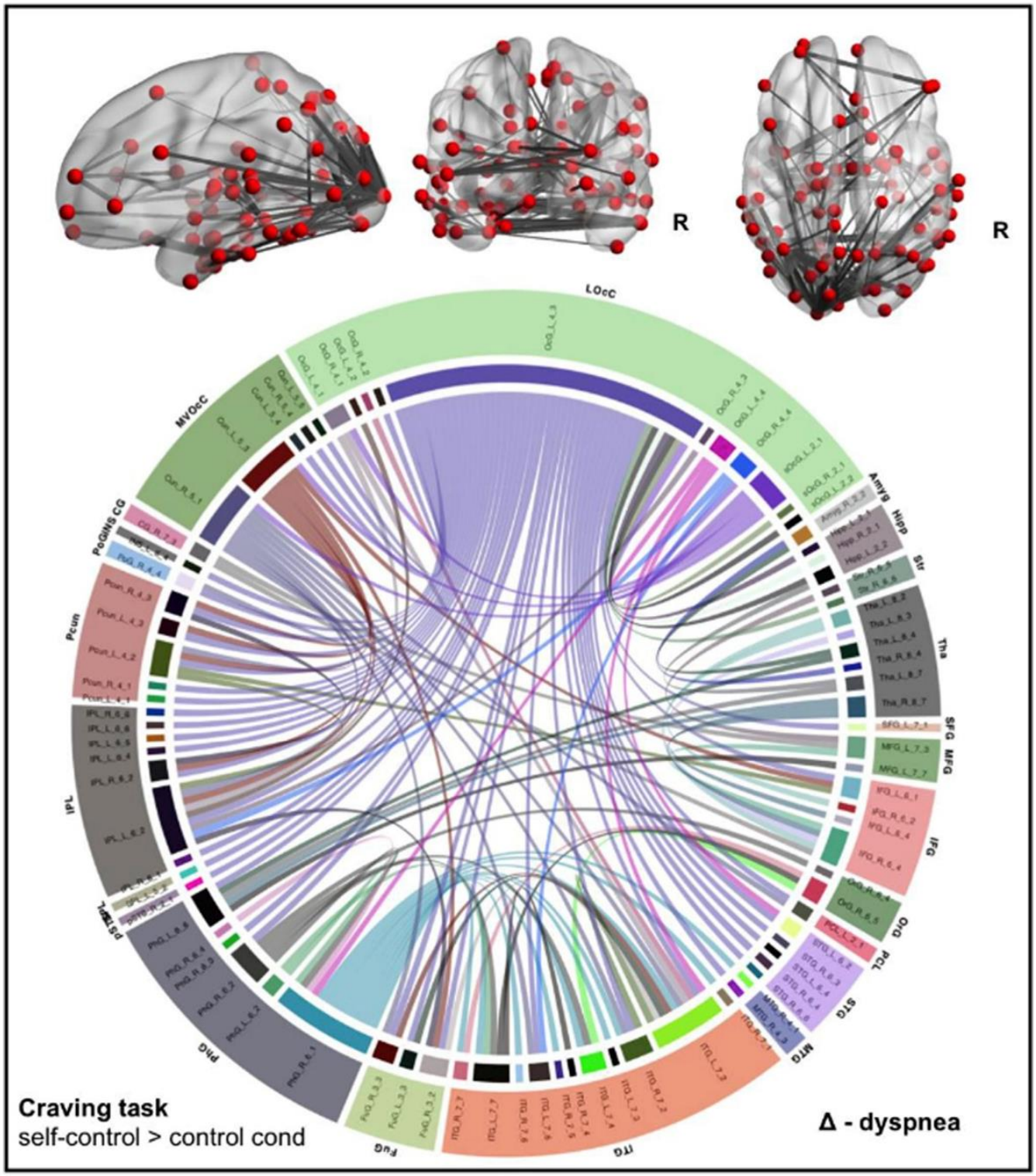

Fig. 18. Network-based statistics revealed a network of 82 regions in which the connectivity was significantly negative correlated to Δ-dyspnea during the down-regulation of craving ($p < .001$, FWE-corrected). This network included among others the insula, the TPJ and regions of the cognitive control network. Hence, those subjects with the greatest levels of connectivity in this subnetwork during the down-regulation of craving 'over-estimated' their body state (i.e., negative prediction error) during the breathing task. Line thickness indicates strength of correlation between Δ-dyspnea and connectivity. Abbreviations from Brainnetome atlas (see BNA subregions file in the supplement).

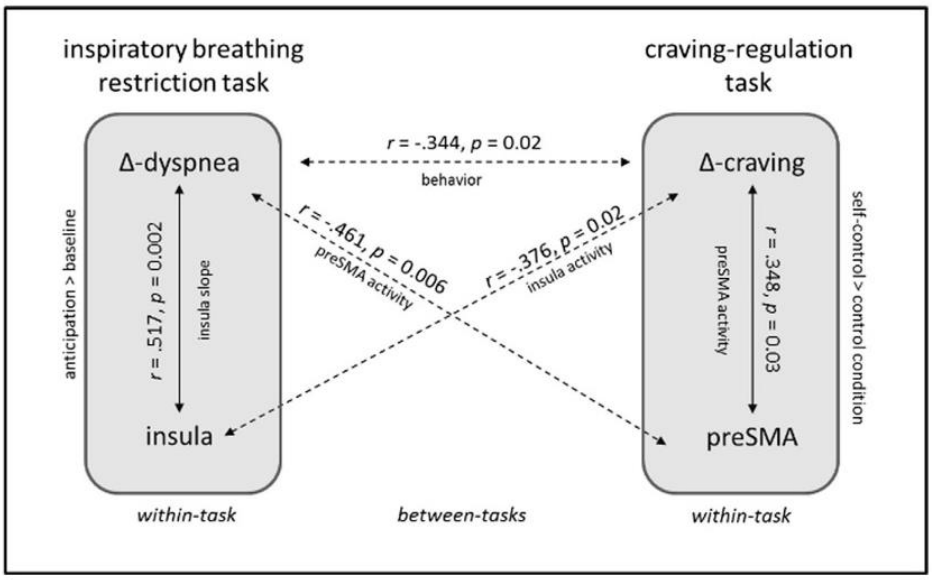

Fig. 19. Summary figure of within and between task-activity brain-behavior relationships incorporating the insula and presupplementary motor area (preSMA) as candidate regions underlying the replicated association between aversive interoceptive predictive models (Δ-dyspnea) and self-control (Δ-craving). These regions emerged an a-priori determined analysis scheme in which we (1) conducted analyses of within-task main effects and determined significant peak-voxel activity of the corresponding contrasts, (2) examined which significant peak-voxels of the previously determined task main effects showed significant within-task brain-behavior relationships (i.e., correlations to the collected task specific behavioral measures), (3) used these regions to compute between-task brain-behavior correlations mirroring the behavioral associations between the inspiratory breathing restriction task and the craving-regulation task. Of the listed correlation coefficients, only the association between the insula slope and Δ-dyspnea remained significant when correcting for the total amount of multiple comparisons (either within- or between task; c.f., Tables 5 and 7). Note, that we did not generate a summary figure for the layer of task-connectivity due to the high complexity and size of the resulting networks.

Nieuwenhuys, 2012; Seth, 2013; Namkung et al., 2017). Its hub function is also supported by recent meta-analyses of regions or network brain dysfunction related to psychopathology that almost always include the insula (e.g., McTeague et al., 2017). It is suggested to play a crucial part in predictive processing across different domains such as the anticipation of pleasant and aversive stimuli (Lovero et al., 2009; Carlson et al., 2011; Kruschwitz et al., 2018a), anticipation of gains and losses (Cho et al., 2013), and in intuitive decision-making-tasks (Dunn et al., 2010; Werner et al., 2013). Thus, its engagement across the inspiratory-breathing-restriction task and the craving-down regulation task could be interpreted in line with the assumption that it may create processing advantages in tasks that refer to the prediction of future internal states. However, to our great surprise, the direction of the observed brain-behavior relationship in the breathing task was reversed to what we had expected. Specifically, we hypothesized that higher levels of interoceptive prediction would be accompanied by stronger engagement of the AI in anticipatory activity and connectivity with its respective network. To the contrary, we found that higher levels of interoceptive prediction were associated with a weaker slope of AI activity (and relatively weaker TPJ activity) in response to the aversive state.

One solution to understand these seemingly conflicting neural patterns between tasks in light of the positive association of interoceptive predictability and self-control could be to interpret observed brain-behavior correlations as a function of task demand and neural efficiency. Specifically, the neural efficiency hypothesis (Neubauer and Fink, 2009) assumes that high performer, as opposed to low performing individuals, would show less neural activation at tasks with reduced task demands, but higher neural activation at tasks with high demands. This phenomenon has been observed across a variety of contexts such as in decision-making tasks (Di Domenico et al., 2015), language processing (Jung et al., 2017), visuo-spatial processing (Guo et al., 2017), and physical exercise (Ludyga et al., 2016). With respect to the tasks employed in this current study, the breathing task can be characterized as a task with relatively low demands (i.e., passive anticipation), whereas the self-control task requires strong self-regulation efforts to actively down-regulate craving in response to tempting snacks via future thinking. Following this framework, one would suspect that those individuals who have more self-regulation capacities may show enhanced neural processing during the craving-task but would recruit less neural resources during the passive anticipation of an aversive internal state as opposed to individuals with fewer self-regulation capacities. Interestingly, patterns in our data align with this conclusion: individuals with negative interoceptive prediction errors (anticipation > experience) as opposed to subjects with positive prediction errors (experience > anticipation) engage the AI (and TPJ) relatively less during anticipation of the aversive internal state (i.e., reduced AI slope and TPJ activity; less AI integration in the self-regulation network with preSMA), but are better able to exert self-control in the craving-task with stronger recruitment of the AI together with the self-regulation network. Most importantly, the existence of this task-demand specific pattern continues when directly linking behavioral and neural responses across the two tasks. Specifically, we observed that higher levels of dorsal AI activation during the anticipation of the aversive interoceptive state (breathing restriction) were significantly associated with lower levels of self-controlled behavior in the craving task. This observation ties with recent suggestions that the dorsal (and not the ventral) insula is involved in the processing of motivational states associated with specific actions (Wager and Barrett, 2017). Conversely, negative prediction errors (anticipation > experience) measured during the breathing task were associated with more activation in the preSMA during the down-regulation of craving, whose anticipatory activity in turn was positively correlated with self-control success (see Fig. 19). This sequence of results can again be interpreted in line with previous findings of Berner et al. (2018) demonstrating insular hypoactivity during the anticipation phase of the breathing restriction task in recovered AN patients who can be characterized by a history of elevated self-control behavior in the context of foods.

When relating levels of interoceptive prediction to connectivity during craving-downregulation we observed a picture consistent with the effects described in the previous paragraph. Specifically, we found that negative prediction errors measured during the breathing task (anticipation > experience) were associated with stronger connectivity in a network during the self-control task including among other areas the insula, TPJ and regions of cognitive control. Surprisingly, when

correlating the level of self-control success to functional connectivity in the breathing task, we found a subnetwork that was also comprised of stronger connectivity between (among other areas) the insula, preSMA and TPJ. According to the neural efficiency hypothesis, we would actually expect that better self-control (therefore also 'over-estimations' of the body state) is related to less connectivity in such a network because individuals high in self-regulation may respectively recruit less resources in the passive anticipation task (c.f., in the breathing task alone we observed that better interoceptive prediction was associated with relatively less insular engagement). What could that mean? The most probable speculation relates to the fact that scores of craving down regulation are a marker of relatively more demanding processing as compared to dyspnea scores. Thus, when regressing these scores to connectivity as measured in the interoception task, one may observe a subnetwork that could be coupled in a more demanding context of interoceptive anticipation in individuals with high self-regulation capacities (i.e. the insula may be recruited alongside regions of self-regulation as preSMA and TPJ).

Although we specified the TPJ as a region of interest explicitly for the craving-regulation task, we did not observe its engagement with respect to anticipatory task activity during application of self-control. However, the TPJ was revealed as being engaged by our data-driven connectivity analyses in both, the craving-regulation task and the breathing task, and was also identified as part of anticipatory networks across-task analyses. Moreover, we found this region whole-brain corrected during the anticipation of the breathing load and also observed that its activity was associated with interoceptive prediction (behaving in the same direction as the insula during the breathing task). As mentioned above, recent meta-analytic evidence pointed towards the role of the right TPJ as a key region in the self-regulation network facilitating emotional regulation and domain-specific self-control of food craving (Han et al., 2018; Langner et al., 2018). Apart from that, the TPJ has been extensively linked to the computation of mental representations, mentalizing, and perspective change in theory of mind research (Frith and Frith, 2006; Saxe, 2006). Recent work (Ondobaka et al., 2017) linked theory of mind to interoceptive inference and speculated about the role of associated regions such as the TPJ in this process. As we observed a strong correlation of TPJ and interoceptive prediction during the breathing task, it could be speculated that the TPJ may also be involved when mentalizing ones future interoceptive states, thereby forming a hub region that potentially facilitates information transfer between the interoceptive and self-regulation system. However, as this is the first description of TPJ in such a context, a profound interpretation of these observed associations cannot be given at this stage of research as more studies are necessary to replicate and elucidate these findings.

While the brain regions discussed in detail in the previous paragraphs (i.e., insula, preSMA, TPJ) correspond to the set of regions resulting in parallel in the a-priori determined analyses schemes (i.e., task activation and task connectivity analyses; see 2.6), it has to be noted that the data-driven connectivity approach resulted in spatially distributed networks that encompassed a wide array of areas that were not specifically hypothesized before hand. Thus, it seems nearby to speculate that the observed association of interoceptive prediction and self-control may be realized through combined interactions of brain regions in distributed networks rather than only by the insula, preSMA, and TPJ. In fact, recent research pointed to evidence for the existence of large-scale intrinsic brain systems supporting interoception in humans (Kleckner et al., 2017) and also showed that self-control is not only realized by single regions but whole networks (e.g., Steimke et al., 2017; Kruschwitz et al., 2018b). Therefore, future research should put emphasis on investigating large-scale network effects contributing to the association of interoception and self-control (e.g., using graph theoretical methods, which is beyond the scope of this current article.

This study contains limitations. First, although we could replicate our previous observation of the association of interoceptive predictions and self-control, the effects that were observed in the current fMRI study are weaker as in our behavioral study. Moreover, as compared to the previous study, anticipated and experienced dyspnea scores showed a smaller variance across individuals (i.e., being rated as more equal). We suspect that the inspiratory breathing restriction setup in the scanner environment may have been perceived as distressing and therefore may have caused these 'ceiling-effects' when rating experience and anticipation. To prevent this effect, future studies could familiarize the subjects with the breathing equipment in a mock scanner or invest more time for habituation of the setup. Second, although we had an a-priori analysis plan that was strongly motivated by our hypotheses, we must acknowledge that when correcting for multiple comparisons with respect to (1) the total amount of ROIs per experiment in the layer of task-activation analyses, (2) the amount of within-task brain behavior correlational analyses, and (3) the amount of between task comparisons, some of the reported and discussed findings did not remain significant (c.f., Tables 5 and 7). Specifically, it is noteworthy that although we hypothesized the insula as a shared neural substrate in both, the breathing restriction and the self-control task, its anticipatory activity in the craving task did not remain significant when correcting for the number of total ROI comparisons (however, we observed its engagement with FWE-corrected task-connectivity) and that none of the between-task brain-behavior relationships would remain significant. As this is the first neuroimaging study that examined the neural substrates underlying the association of interoceptive predictions and self-control, we investigated a wide range of potentially associated brain regions, which in turn led to the relatively large number of associated correlational analyses within and across experiments and therefore increased the potential of inflated Type I error rates. Thus, future studies should aim for targeted replications of the presented collection of effects to confirm our findings. Third, interoceptive predictions in our experiments were based on a much shorter time scale than interoceptive predictions associated with long-term homeostatic goals. However, as we observed the effect not only between experiments 1 and 2 but also to a trait measure of self-control, it seems tempting to speculate that a common underlying mechanism extends across different time-scales independent of how fast aversive feedback was learned to update future behavior. Forth, although we assessed an experimental measure of self-control (i.e., craving-downregulation) and a trait measure of self-control, we did not provide any choice alternatives to act self-controlled (e.g., temptation-conflicts). Thus, future studies should bridge this gap by using decision-making tasks that specifically involve the interoceptive system. In the context of task-design, it is noteworthy that the currently implemented craving regulation task depends solely on self-reported craving. Possibly, for future research, more implicit measures could also be considered to study the observed effects in more objective way (for example, the amount of snacks available consumed as in Hofmann et al., 2009). Finally, a major limitation must be seen in the fact that information on BMI and substance misuse is not available for this study. Although recent research showed that obesity and drug-usage are associated with altered interoceptive processing, which in turn may contribute to impaired self-control or eating-behavior (Paulus, 2007b; Simmons and DeVille, 2017), we cannot exclude the possibility that other factors associated with these nuisance variables altered our observations. Thus, future studies should collect respective data to rule out any moderating effects.

Taken together, we suggest that self-controlled choices may be interpreted as active inference aiming to change the state of the body so it becomes congruent with one's long-term homeostatic goals. When we make choices, we need to anticipate future interoceptive states linked to decision outcomes and compare them to the internal homeostatic model. Only if we're in a position to predict the interoceptive consequences of a decision, can we effectively minimize interoceptive prediction errors that relate to our long-term homeostatic goals (c.f., Kruschwitz et al., 2019). In line with this suggestion, we can replicate our previous observations and again demonstrate that two measures of self-control (i.e., successful craving reduction and trait self-regulation) relate to the degree to which an individual generates predictive models of her or his own future

interoceptive states. We extend our previous study by showing that the AI and preSMA could be candidate brain regions underlying this behavioral relationship possibly creating processing advantages in self-control situations referring to the prediction of future internal states. Based on these observations, it seems conceivable that interoceptive interventions as mindfulness techniques (or other interventions aimed at altering interoceptive and insular processing as discussed in detail in Paulus et al., 2019), may help improving self-controlled behavior in the clinical setting. Specifically, negative interoceptive prediction errors (anticipation > experience) and elevated self-corrective behavior (e.g. pathologic self-control in eating disorders) could be minimized or corrected by shifting attention away from the predicted body state and towards the observed body state (c.f., Farb et al., 2015). Vice versa, interventions in drug-dependent individuals could use interoceptive trainings to accurately register aversive feedback with the aim to downweigh insular response to goal-directed drug seeking and to updating future behavior (Paulus, 2007b).

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Declaration of competing interest

HW received a speaker honorarium of Servier.

CRediT authorship contribution statement

Henrik Walter: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing - original draft, Funding acquisition, Writing - review & editing. **Anne Kausch:** Conceptualization, Formal analysis, Investigation, Methodology, Writing - original draft, Project administration, Validation, Data curation, Writing - review & editing. **Lena Dorfschmidt:** Investigation. **Lea Waller:** Investigation, Software. **Narges Chinichian:** Visualization. **Ilya Veer:** Software, Formal analysis, Methodology. **Kevin Hilbert:** Supervision, Methodology. **Ulrike Lüken:** Supervision, Resources. **Martin P. Paulus:** Conceptualization, Methodology, Supervision, Writing - original draft. **Thomas Goschke:** Conceptualization, Methodology, Supervision, Writing - original draft, Funding acquisition. **Johann D. Kruschwitz:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing, Project administration, Data curation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116841.

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Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste

Kruschitz JD, **Kausch A,** Brovkin A, Keshmirian A, Paulus MP, Goschke T, Walter H. Self-control is linked to interoceptive inference: Craving regulation and the prediction of aversive interoceptive states induced with inspiratory breathing load. Cognition. 2019 Dec 1;193:104028.

- Impact Factor: 3,354

Walter H*, **Kausch A***, Dorfschmidt L, Waller L, Chinichian N, Veer I, Hilbert K, Lüken U, Paulus MP, Goschke T, Kruschwitz JD. Self-control and interoception: Linking the neural substrates of craving regulation and the prediction of aversive interoceptive states induced by inspiratory breathing restriction. Neuroimage. 2020 Jul 15;215:116841. ***(*equal contribution)***

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