

Rest-stimulus interaction in the brain: a review

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Studies in animals and humans have demonstrated intrinsic activity in the brain during the resting state. The concept of the default-mode network (DMN) – a set of brain regions in which resting-state activity (RSA) activity is reduced in response to external stimuli – recently raised much controversy concerning the psychological correlates of RSA. However, it remains unclear how RSA interacts with stimulus-induced activity. Here we review studies in humans and animals that address how RSA interacts with stimulus-induced activity; we also discuss, conversely, how stimulus-induced activity can modulate RSA. Psychologically, the rest–stimulus interaction is relevant to predicting subsequent behavioral and mental states. We conclude that a better understanding of the rest–stimulus interaction is likely to be crucial to the elucidation of the brain’s contribution to mental states.

RSA and stimulus-induced activity

The concept of the DMN was initially introduced to describe a set of regions that show a consistent pattern of deactivation during stimulus- or task-induced activity [1–4]. The regions of the DMN as initially described include anterior and posterior cortical midline regions such as the ventromedial prefrontal cortex (VMPFC), the dorsomedial prefrontal cortex (DMPFC), different parts (sub-, pre-, and supragenual) of the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC) and precuneus, along with certain regions outwith the midline such as the lateral parietal cortex and the hippocampus [5]. While deactivated during stimulus- or task-induced activity, these regions show high activity and a high degree of intrinsic functional connectivity in the resting state [5–9]. As a result of these findings, RSA has recently aroused strong interest and controversy [3] especially in the field of neuroimaging, although the relevance of RSA now extends far beyond this area to the field of neuroscience as a whole, including brain function in animals [10–12].

High RSA has also been observed in DMN regions, including in the sensory cortices, motor cortex, insula, and subcortical regions [2,13–15]. Further support for spontaneous RSA across the whole brain comes from electrophysiological studies showing spontaneous neuronal oscillations and synchronizations in various parts of the brain including thalamus [16], hypothala-

mus (particularly the suprachiasmatic nucleus) [17], the ventral tegmental area and prefrontal cortex [18], hippocampus and visual cortex [19–25]. This suggests that high RSA could be prevalent throughout the whole brain, and this, one might assume, would also impact upon neuronal activity induced by stimuli. However, whereas some studies have investigated the impact of RSA on subsequent stimulus-induced activity [19,26–29], the different forms and the exact mechanisms underlying such rest–stimulus interaction remain unclear.

We here take the DMN and its distinction between task-negative and task-positive regions as a purely heuristic starting point. Based on human imaging studies, task-positive regions show positive signal changes (i.e. activation) during tasks, whereas task-negative regions tend instead to exhibit negative signal changes (i.e. deactivation); both types of regions and signals are supposed to be associated with different physiological and psychological functions, although the exact distinction between them remains unclear (Box 1).

Another issue relevant in this respect is the exact definition of RSA. RSA could refer to the intrinsic activity displayed by the brain itself, and one region well recognized to show intrinsic RSA is the thalamus [30]. Such intrinsic RSA could though need to be distinguished from the RSA that is sustained by the continuous intero- and exteroceptive input from the body and environment, and mirroring what Barry *et al.* [31] call ‘arousal baseline’. However, it remains unclear whether RSA in DMN regions corresponds either to purely intrinsic RSA or to the ‘arousal baseline’. Due to the difficulty in exactly defining the brain’s RSA, we here presuppose a purely operational meaning of the RSA as the activity taking place in the absence of external stimuli arising from outside of the brain itself (e.g. as Shulman *et al.* [26] say ‘an adjective that describes a property of the brain state that exists before a stimulation of interest’; see also Eijsden *et al.* [32]). Even if the exact definition of RSA remains unclear (for further discussion see Conclusion), such operational meaning opens the door to experimental investigation of how the RSA interacts with stimulus-induced activity.

The interaction between brain RSA and stimulus-induced activity can progress in either of two directions. First, RSA could interact with stimulus-induced activity so as to modulate the latter, thus impacting upon resulting

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Box 1. Can we distinguish between task-positive and task-negative regions in the brain?

Distinction: the distinction between task-positive and task-negative regions is based predominantly on observations in human imaging studies [4,29]. Task-negative regions are those that show predominantly negative signal changes (i.e. deactivation) during external stimulation. This has led to the assumption that these regions must show high RSA, allowing only negative rather than positive signal changes during external stimulation. Because task-positive regions show predominantly positive signal changes (i.e. activation) during external stimulation, this has led to the assumption that these regions might not show high RSA.

Methodological issues: we cannot at this point exclude that the often observed anticorrelation between task-positive and -negative regions (see above) could be due to our own way of analyzing the data rather than reflecting the intrinsic properties of the brain itself [68]. Regionally, the distinction between task-positive and -negative regions has also been put into question because regions supposed to be initially task-positive, for instance the hippocampus or the insula, can have features similar to task-negative regions [2]. Hence, the seemingly clear distinction between task-positive and -negative regions must be called into doubt.

Physiological mechanisms: deactivation in task-negative regions can be characterized by negative BOLD responses (NBR) in fMRI that in turn have been associated with neural inhibition and GABA [29]. However, deactivation (and, especially, negative BOLD responses) have been shown not to be restricted to task-negative regions, and can also be seen in several task-positive regions, including sensory regions such as the visual cortex. One might also suggest that neural inhibition and GABA-mediated inhibitory neurotransmission also operate in task-positive regions, as was indicated by a combined fMRI-MRS study in human [37]. Hence, the seemingly physiological distinction between task-positive and -negative regions with regard to NBR and associated neural inhibition and GABA must be put into doubt.

Psychological correlates: task-negative regions are often associated with self-relatedness [69], consciousness [70], mind-wandering [61,62] and episodic memory retrieval [2]. However, such regional specificity has been called into question because all four functions are associated with both task-negative regions and task-positive regions [61]. This makes the attribution of any specific psychological functions to task-negative regions, as distinct from task-positive regions, rather problematic.

Operational determination: due to the apparent methodological, regional, physiological and psychological non-specificity of task-negative regions, we have proposed the distinction between task-negative and task-positive regions in a purely heuristic sense. Our use of this distinction is heuristic in the sense that we do not associate principal physiological, regional, or psychological differences with task-positive and -negative regions. We only use this distinction to distinguish between different types of rest-stimulus interaction – and whether such distinction between different types of rest-stimulus interaction really mirrors the way the brain itself distinguishes different rest-stimulus interactions, or instead reflects our way of observing, analyzing and categorizing them, must remain open at this point.

behavioral and/or mental states. Conversely, stimulus-induced activity might interact with and modulate the RSA, altering in some way this basal level of activity. We consecutively divide our review into two main sections dwelling on rest-stimulus interactions and stimulus-rest interactions. Because the reported studies mostly rely on imaging methods, we here use the imaging-based concept of the DMN including the distinction between task-negative or task-positive regions as heuristic starting point to distinguish between different forms of rest-stimulus and stimulus-rest interactions (Tables 1,2; Figures 1,2).

Rest-stimulus interaction I. Modulation of stimulus-induced activity by the resting state

How is stimulus-induced activity predicted by RSA in task-negative regions?

High RSA in human imaging studies has been observed especially in the task-negative regions of the DMN. This raises the question how the high RSA in these regions impacts upon stimulus-induced activity and the respectively associated behavioral and mental states. We hence discuss several studies that investigate the various facets of such rest-stimulus interaction.

Using combined magnetic resonance spectroscopy (MRS) and fMRI [29], a recent study investigated the level of γ -aminobutyric acid (GABA) in a typical task-negative region, the perigenual anterior cingulate cortex (PACC), that is part of the DMN that shows a predominant negative blood oxygen level dependent (BOLD) response (NBR). The resting-state level of GABA in the PACC correlated with the degree of NBR in the same region induced by an emotional judgment task. The resting-state concentration of GABA in the PACC correlated positively with the degree of NBR during stimulus-induced activity. This study demonstrated that the resting-state concentration of GABA in the PACC, a task-negative region, could indeed impact upon stimulus-induced activity changes in the same region PACC (see Buzsáki *et al.* [33] and Jacob *et al.* [34] who review how GABA and neural inhibition are related to neuronal activity and brain function).

Another question arising pertains to how the level of RSA in task-negative regions affects the stimulus-induced activity in task-positive regions. This was first shown in a study by Greicius *et al.* [5] who investigated how the DMN, the task-negative network, impacts upon subsequent stimulus-induced activity in visual and auditory tasks during passive sensory tasks within each subject (e.g. with modulation of the task). They observed that the level of activity in the DMN during stimulation predicted the neuronal activity in both visual and auditory cortices during the auditory and visual tasks. The lower the activity in the task-negative networks of the DMN during auditory/visual stimulation, the higher the stimulus-induced neuronal activity in auditory and visual cortex. Hence, the level of RSA in the task-negative regions of the DMN can modulate the levels of stimulus-induced neuronal activity in task-positive regions.

In an animal-based study Maandag *et al.* [28] used anesthetic drugs (halothane and chloralose, that are thought to act, at least in part, via GABA receptors) to elicit different levels of RSA in rats, and used fMRI to measure neural activity during subsequent forepaw stimulation. High RSA levels were associated with widespread activity across the cortex and rather weak evoked activity in sensorimotor cortex during the forepaw movement. This activity pattern was reversed in low RSA, where neural activity was stronger in the sensorimotor cortex but more or less absent in other cortical regions. These results demonstrate that the level of RSA can modulate the distribution and intensity of stimulus-induced activity in the same (i.e. task-negative) region, as well as in other (i.e. task-positive) regions such as the sensorimotor cortex (see

Table 1. Summary of brain regions and measures in studies reporting modulation of stimulus-induced activity by RSA

Independent variable: rest		Dependent variable: stimulus		Refs
Region	Measure	Region	Measure	
pACC (TN)	GABA	pACC (TN)	NBR	[29]
Whole brain	Glutamate	Somatosensory cortex (TP)	PBR	[28]
DMN (TN)	Deactivation	ns	Sensory perception	[27]
DMN (TN)	Activation	Visual and auditory cortex	PBR	[5]
Somatosensory cortex (TP)	Activation	Somatosensory cortex (TP)	PBR	[35]
Visual cortex (TP)	GABA	Visual cortex (TP)	PBR	[37]
Cat visual cortex (TP)	Voltage-sensitive dye imaging	Cat visual cortex (TP)	Voltage-sensitive dye imaging	[19]
ns	Phase of spontaneous EEG oscillations	Visual and auditory cortex	ERP	[31,38–44]
Dorsal parietal, visual extrastriate and prefrontal cortex (TP)	BOLD signal	ns	Motion discrimination judgement	[49]
ACC and the LPFC (TP)	BOLD signal	ns	Visual attention task	[50]
Insula, ACC (TP)	BOLD signals	ns	Pain	[27]
Somatomotor cortex (TP)	BOLD signal	ns	Button press	[36]
ns	Alpha and theta bands (EEG)	ns	Light perception	[51]

ACC, anterior cingulate cortex; DMN, default-mode network; EEG, electroencephalography; ERP, event-related potentials; GABA, γ -aminobutyric acid; LPFC, lateral prefrontal cortex; NBR, negative BOLD response; pACC, perigenual anterior cingulate cortex; PBR, positive BOLD response; TN, task-negative region; TP, task-positive region; ns, not specified.

Table 2. Summary of brain regions and measures in studies reporting modulation of RSA by stimulus-induced activity

Independent variable: stimulus		Dependent variable: rest		Refs
Region	Measure	Region	Measure	
ns	Visual perceptual learning	DMN (TN), visual cortex, fronto-parietal regions	Resting state connectivity	[57]
ns	Motor learning	Lateral frontal and parietal regions and the cerebellum (TP)	PBR	[60]
ns	Motor training	Primary motor cortex, SMA (TP)	Functional connectivity	[59]
ns	Working memory load	DMN (TN)	PBR	[54]
ns	High and low self-relatedness	MPFC, PCC (TN)	PBR	[56]
Visual cortex (TP)	Voltage-sensitive dye imaging	Visual cortex (TP)	Voltage-sensitive dye imaging	[58]

DMN, default-mode network; ERP, event-related potentials; MPFC, medial prefrontal cortex; PBR, positive BOLD response; PCC, posterior cingulate cortex; SMA, supplementary motor area; TN, task-negative region; TP, task-positive region; ns, not specified.

also Shulman *et al.* [26] and Eijsden *et al.* [32] for discussion of the results by Maandag on a conceptual level).

With the above evidence clearly demonstrating that RSA in task-negative regions does influence stimulus-induced activity, the question arises as to what effect this has on behavior related to the stimulus-induced activity. This was addressed by Boly *et al.* [27] who investigated the impact of RSA in task-negative (and task-positive) regions on subsequent behavioral performance in a somatosensory perception task. The investigators applied stimuli (a laser to the hand) with different degrees of awareness and pain. They then investigated whether the RSA (3 seconds before the stimulus onset) in task-negative and task-positive regions could predict the subsequent perception, noted by the degree of awareness and feeling of pain. Interestingly, decreased RSA in task-negative regions of the DMN (the PCC/precuneus, the temporal parietal junction, and the parahippocampal

region) exerted a facilitating effect upon subsequent perceptual awareness.

Taken together, these studies demonstrate that RSA in task-negative regions of the DMN seems to be relevant for stimulus-induced activity and the associated behavioral and mental states. What though remains unclear is whether the RSA in the task-positive regions themselves also impacts upon subsequent stimulus-induced activity in the very same regions.

How is stimulus-induced activity predicted by RSA in task-positive regions?

In addition to task-negative regions, high RSA has also been observed in regions outside the DMN and thus in task-positive regions. Does RSA in these regions also modulate subsequent stimulus-induced activity and the respectively associated behavioral and mental states? Hence the focus shifts now to the RSA of task-positive regions.

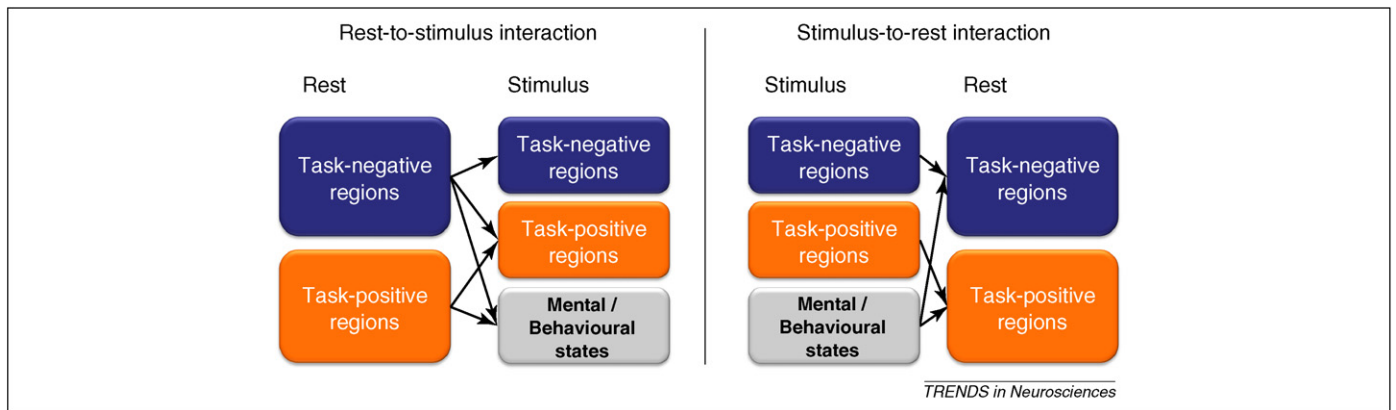


Figure 1. Different types of rest–stimulus interaction. The figure shows the various forms of possible rest–stimulus interactions across the same or different regions. We distinguish here between the impact of resting-state activity (RSA) on subsequent stimulus-induced activity (rest-to-stimulus interaction), and the modulation of RSA by stimulus-induced activity (stimulus-to-rest interaction). For heuristic purposes we also distinguish between task-positive (shown in orange boxes) and task-negative (shown in blue boxes) regions based on the findings of the DMN as revealed by human neuroimaging. The grey boxes indicate mental or behavioral states of the subject investigated.

One study investigated how resting-state neuronal oscillations impact upon subsequent behavior. Fox *et al.* [35] observed that the ongoing neuronal oscillations in the somatomotor cortex, that persisted during stimulus-induced activity, correlated with a high percentage of trial-to-trial variability in a somatomotor cortex task-related activity and button-press behavior. A subsequent study (Fox *et al.* [36]) demonstrated that intrinsic fluctuations in the left somatomotor cortex predicted trial-to-trial variability in button-press force, thus linking RSA directly to behavior. Spontaneous BOLD fluctuations and task-related responses in the somatomotor cortex could be superimposed in a linear fashion; this clearly indicates the functional and behavioral significance of intrinsic RSA in task-positive regions.

Another study investigated the resting-state concentration of GABA in the visual cortex and its correlation with subsequent stimulus-induced activity (BOLD) and gamma frequency firing in the visual cortex [37]. They measured resting-state levels of GABA in the visual cortex with MRS and employed fMRI and magnetoencephalography (MEG) to measure stimulus-induced activity changes in the visual cortex. The resting-state concentration of GABA in the visual cortex predicted the degree of stimulus-induced activation (i.e. positive BOLD response) and gamma frequency activity in the very same region. Hence, the RSA level preceding the actual stimulus-induced activity seems to be crucially related to neuronal activity during stimulation, although the exact mechanisms, either direct-causal or indirect-modulatory, remain to be explored.

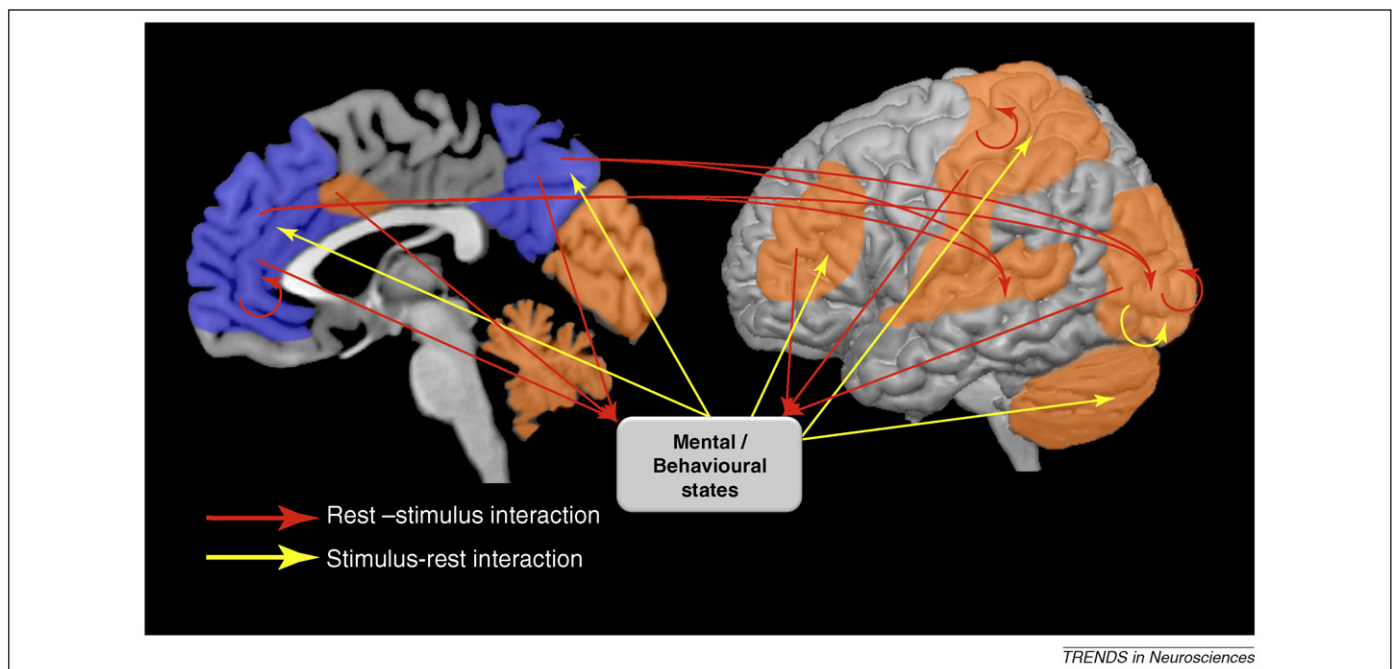


Figure 2. Regions implicated in studies on rest–stimulus and stimulus–rest interactions. The figure shows the different regions reported in studies discussed in the text. Task-negative regions are colored in blue, task-positive regions are colored in orange. Red arrows indicate the modulation of stimulus-induced activity by RSA, and yellow arrows indicate modulation of RSA by stimulus-induced activity. The grey box shows mental/behavioral states that have been inferred as dependent variable in studies on rest–stimulus or stimulus–rest interactions.

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Although not presupposing the distinction between task-positive and task-negative regions, EEG studies demonstrate that the phase of spontaneous EEG oscillations modulates the amplitude of subsequent stimulus-induced activity in auditory or visual cortex as measured by event-related potentials (ERPs) [31,38–44]. Also using electrophysiological measurements, Smallwood *et al.* [45] investigated the effects of preceding ‘mind-wandering’ in the resting state on stimulus-induced P300 activity, an electrophysiological indicator of cognitive processing. They observed a reduction in the amplitude of the P300 during stimulus-induced activity following self-reported mind-wandering.

The assumed modulation of stimulus-induced activity by the RSA is further supported by data from animal studies. Fiser *et al.* [46] investigated resting young and adult ferrets during the presentation of natural-scene and random-noise film images. Whereas the correspondence between stimulus-induced neuronal activity in the visual cortex and the degree and spatial extension of the neuronal representation of the input signal was weak in young ferrets, it improved with age. This improvement could be traced back to a shift in the dynamics of spontaneous firing in the visual cortex. These results suggest a central developmental role for RSA.

A series of studies investigated the dependence of stimulus-induced activity in cat visual cortex on RSA levels [19,47,48]. The variability of stimulus-induced activity in single neurons (i.e. trial-to-trial variability) could be predicted by their spontaneous firing rates in the resting state. This clearly indicates that even stimulus-induced activity at the level of the single visual cortical neuron is modulated by RSA in visual cortex.

The RSA in task-positive regions also has an impact upon subsequent behavioral and psychological states. Sapir *et al.* [49] investigated the impact of changes in the spatial attention cortices, as induced by a cue, on the accuracy of a motion discrimination judgement. Using fMRI, they observed that the level of activity in dorsal parietal, visual extrastriate and prefrontal cortex elicited by a preceding cue (as distinguished from the activity during the task itself) predicted the accuracy in the subsequent spatial discrimination task. Analogously, Weissman *et al.* (2006) demonstrated that slow reaction times in a visual attention task are predicted by reduced prestimulus activity in the ACC and the LPFC [50]. Whereas these studies focus on behavioral parameters (i.e. reaction time and accuracy) as dependent variables, the study by Boly *et al.* [27] described above also demonstrated that RSA in task-positive regions, such as the lateral prefrontal cortex (LPFC), the supragenual ACC, and the medial thalamus, predicted positively the subsequent psychological (or mental) state (i.e. somatosensory awareness or pain). All three studies suggest that the level of RSA in task-positive regions has a strong impact on the behavioral and psychological state associated with stimulus-induced activity, although the exact extent of the impact differed according to the type of task and the brain regions studied.

Busch *et al.* [51] presented brief flashes of light at the individual luminance (i.e. detection) threshold while EEG was recorded. When comparing phase distributions shortly

before stimulus onset (800–0 ms) between hits and misses, they showed different phase angles that were strongest in the alpha and theta bands. They also observed that stimuli preceded by a strong alpha frequency were less likely to be detected. This suggests that, depending on the phase of neuronal oscillations and the amplitude of alpha frequency in the resting state, some moments could be conducive to perception – the authors describe these as ‘perceptual moments’ (see also Smith *et al.* [52]).

An animal study investigated the unconditioned reflex in the third eyelid (the nictitating membrane) of rabbits in response to stimulation by a puff of air [53]. The animals learned to close the nictitating membrane prior to the air puff when that stimulus was preceded by a neutral stimulus such as a sound. Both stimulus-features (i.e. timing with temporal gap between unconditioned and conditioned sounds and their strength/intensity) as well as the resting-state activity of the hippocampus (i.e. amplitude of its theta oscillations) positively predicted the speed of the learning effects and hence the pace of conditioning.

Taken together, these studies demonstrate that RSA in task-positive regions has a clear impact upon subsequent stimulus-induced activity in task-positive regions and/or associated behavioral and mental states.

Rest–stimulus interaction II. Modulation of RSA by stimulus-induced activity

How is RSA in task-negative regions modulated by stimulus-induced activity?

We have so far investigated the impact of RSA on subsequent stimulus-induced activity. However, the interaction could also function in reverse, with stimulus-induced activity modulating RSA. We start by describing studies addressing the impact of stimulus-induced activity on RSA in task-negative regions.

A study by Pyka *et al.* [54] investigated DMN activation using an ‘n-back’ working-memory task (where the subject is presented with a sequence of stimuli and determines if the current stimulus matches that from n steps earlier in the series). DMN activity in 1-back and 2-back blocks was compared to activity levels in a 0-back block. Activity levels in the DMN regions were significantly higher during resting-state periods following the 1- and 2-back tasks than following the 0-back task. This suggests that subsequent RSA is differentially modulated by the different demands of the preceding working memory task, thereby indicating stimulus–rest interaction.

Analogously, Lowe *et al.* [55] demonstrated that the resting-state connectivity (i.e. low-frequency oscillations) between task-positive regions, such as the right dorsolateral prefrontal cortex, the middle frontal gyrus/lateral premotor cortex and the inferior parietal lobule, was significantly enhanced during execution of a working-memory task.

A recent study investigated how the psychological features of preceding emotional picture perception predicted the degree of activity in a subsequent resting-state period [56]. The analysis then compared all of the resting-state periods that followed a high self-related stimulus versus those following a low self-related stimulus. This yielded significant RSA differences in several task-negative

regions (i.e. VMPFC, DMPFC, PCC). Whereas the specific effects of self-relatedness (as distinguished from those of emotions) in the subsequent resting-state period involved midline regions, stimulus-evoked effects of self-relatedness during the stimulus period itself implicated subcortical regions (i.e. periaqueductal gray matter (PAG)/tectum, ventral striatum, amygdala).

Taken together, these studies demonstrate that stimulus-induced activity in regions either inside or outside the DMN can modulate the level of RSA in task-negative regions. However, due to the low number of studies this conclusion must be considered preliminary.

How is resting state activity in task-positive regions modulated by stimulus-induced activity?

Stimulus-induced activity might not only modulate RSA in task-negative regions (and hence the DMN itself) but also in task-positive regions, be it the same region or another region. Some recent studies have addressed this possibility.

Lewis *et al.* [57] investigated the effects of visual perceptual learning on resting-state connectivity. Subjects underwent training in a shape-identification task constrained to one visual quadrant, and were followed by fMRI. This revealed an effect of training on visual cortex activation on the respective side (i.e. quadrant) when compared to the untrained side. After training, changes in resting-state connectivity between the visual cortex and other regions including task-positive (e.g. fronto-parietal regions involved in spatial attention) and task-negative (e.g. DMN) regions were observed.

Analogous effects have been observed in rat visual cortex [58]. The repetitive presentation of a visual stimulus induces not only stimulus-induced activity in the visual cortex but also impacts upon subsequent spontaneous ongoing activity in the same region. The spatiotemporal patterns of the stimulus-induced activity closely resembled the subsequent pattern of spontaneous activity and hence the RSA in the visual cortex. The authors called this 'wave-mediated reverberation' and suggested that it might contribute to the consolidation of the transient effects of sensory experience into long-lasting cortical modifications.

Newton *et al.* [59] observed that the functional connectivity of the primary motor cortex to other regions (cerebellum, auditory, SMA) increased during motor tapping when compared to resting state. Another study investigated the effects of motor learning on RSA [60]. Neural activity in lateral frontal and parietal regions and the cerebellum was significantly increased after a visuomotor training session when compared to before the session. Interestingly, the same network was not recruited during mere motor performance, thus the increased activity was specific for motor learning.

Conclusion

We here reviewed the various forms of how brain RSA can interact with and modulate stimulus-induced activity. The overview clearly suggests that there are multiple types of interactions between RSA and stimulus-based activity, and these interactions can be detected in different regions across the whole brain, and including both task-positive and task-negative regions. Most importantly, rest–

stimulus interactions appear to occur in both directions, from rest to stimulus and from stimulus to rest.

One crucial question concerns the psychological correlates of such interactions. Stimulus–rest interaction could for instance correspond to learning effects. The studies described above demonstrated learning effects in task-positive regions outside the DMN as distinguished from the regions involved in the actual performance. What though remains to be demonstrated is whether learning also affects the activation and connectivity in task-negative regions of the DMN. Another psychological correlate underlying stimulus–rest interaction could be that subjects might ruminate about the stimulus during a subsequent resting-state period (for instance by imagining the stimulus): if so this could suggest that mind-wandering (see Christoff *et al.* [61] and Mason *et al.* [62]) and mental imagery are increased following a stimulus period, but this has not yet been demonstrated.

At the neuronal level the biochemical mechanisms underlying such interactions between RSA and stimulus-induced activity remain unclear. Two studies suggested that GABA could play a central role in mediating such effects, but other transmitters could certainly be involved. Other questions concern the developmental and psychiatric relevance of such interactions. The DMN has been shown to be already present in infants and children [63–65]. How the connectivity of the DMN is shaped and whether DMN activity could mediate possible learning effects in children remains unclear. Furthermore, it is not known if developmental disturbance of the DMN could possibly lead to later psychiatric abnormalities such as schizophrenia. It is however clear that RSA and connectivity within the DMN could be of special developmental as well as psychiatric significance, for instance in schizophrenia (reviewed by Broyd *et al.* [1]) and in depression [66,67].

Methodologically, most of the results described above rely on human imaging and more specifically on fMRI. However, because the BOLD response in fMRI is rather sluggish, clear-cut experimental separation between RSA and stimulus-induced activity changes can be difficult. Hence, techniques other than fMRI could be more suitable for RSA studies: for instance the background noise in EEG

Box 2. Outstanding questions

- What are the psychological correlates of rest–stimulus and stimulus–rest interactions? Are learning, mind-wandering or some other functions possible psychological correlates?
- What neuronal mechanisms underlie the bilateral interaction between resting-state activity and stimulus-induced activity?
- How do rest–stimulus and stimulus–rest interactions shape brain development in infants and how do they influence or reflect their mental states?
- Are psychiatric disorders such as schizophrenia and depression associated with abnormal rest–stimulus or stimulus–rest interactions?
- How can we investigate rest–stimulus and stimulus–rest interactions by techniques other than fMRI?
- How can we define and operationalize RSA, and how is it related to the neural processing of interoceptive stimuli originating within the body?

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or MEG recordings is not as extensive as in fMRI. Finally, one can discuss the functional correlates of RSA. Does high RSA merely reflect suspension of functional activity, or does it instead represent some specific functions that are continuously operating in the background? This issue is obviously closely tied to the exact definition of RSA, whether to define it as purely intrinsic or as 'arousal baseline' (see Introduction). Whereas the above described studies on rest–stimulus and stimulus–rest interactions clearly concern the arousal baseline, the impact of stimuli on intrinsic RSA as well as the interaction between the two kinds of RSA remains unclear. The answers to these and other outstanding questions (Box 2) could not only improve our understanding of the role of RSA but, even more importantly, are likely to provide new insights into how the brain operates in general.

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