

COMMENTARY

The Units Of Thought

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ABSTRACT: That associative processing provides the vehicle of thought is a long-standing idea. We describe here observations from cognitive neuroimaging that elucidate the neural processing that mediates this element. This account further allows a more specific ascription of a cognitive function to the brain's "default" activity in mindwandering. We extend this account to argue that one primary outcome of associative processing is the generation of predictions, which approximate the immediately relevant future and thus facilitate perception, action, and the progression of thought. © 2007 Wiley-Liss, Inc.

KEY WORDS: default network; associations; medial parietal; medial prefrontal; parahippocampal cortex

INTRODUCTION

To examine human thinking, we will concentrate on the processes that occupy the cognitive brain when it is not engaged in an active, goal-directed task. There have been numerous proposals regarding the processes that occupy our minds at such "resting" times: memory consolidation and replaying of past events, planning future actions and simulating possible scenarios, ruminating, fantasizing, etc. We argue that the vast majority of these processes, if not all, depends on the activation of experience-based associations.

We are all too familiar with the frequent mindwandering of thought, where X can be linked to Y in a matter of seconds (e.g., "moon → dark-side → Pink Floyd → high-school → math → physics → Einstein → amusing hairstyle → I need to get a haircut"). Although such associative thoughts are based on unique personal experiences, it seems that the neural mechanisms that mediate them are remarkably consistent across individuals.

Associations go far beyond subserving random walking of thought during otherwise idle intervals. Providing the core element of thought, associations are proposed to be involved in an extraordinarily wide range of processes. For example, they connect information in memory in a way that affords efficient encoding and retrieval. Furthermore, by coactivating associated familiar concepts, explicitly or implicitly, we can cope with uncertainty and resolve ambiguities, think in metaphors and analogies, extract meaning from symbols (Barsalou, 1999) (e.g., road signs,

body-language), guide attention (Moores et al., 2003), form first-impressions, navigate, generate reward-related predictions, and form affective associations between a stimulus and its relevance; processes that are critical for eliciting behavior that promotes survival. Understanding associative processing can also help explain mechanisms of learning, emotional response, addictive behavior, stereotyping, the influence of advertising, and more. In sum, we argue that associations and associative processing can be seen as the primitive building-block of thought.

That associations provide the principle element of human thought is a long-standing idea, dating back at least to Plato, Aristotle, Vives, Hobbes and, later, Locke, Hume and Hartley. We present here a set of observations from cognitive neuroimaging findings that we propose as the neural correlates that support this central idea. As elaborated later, these associations are not necessarily simple Hebbian-like links between related items with a connection that is activated automatically, but rather can be more sophisticated. We discuss the implications of this proposal for associative disorders, including aging and depression.

THE BRAIN'S DEFAULT NETWORK

Although it is common to refer to one's mind as "resting" when it is not engaged in some goal-directed task, brain imaging findings indicate that the brain is highly active even during "task-less" periods. The neural activity that corresponds to such a resting state, termed the *default mode* (Raichle et al., 2001), is currently a subject of intense research. The trigger for the surge in interest in the default network was the repeated observation in neuroimaging experiments that several cortical areas show strong activations when the subjects are supposed to rest (i.e., not perform an experiment-specific task). What is remarkable about this activity is that the same network of regions is active across participants, despite the fact that they are typically being told, in a rather undirected instruction, to "rest quietly" (Shulman et al., 1997; Binder et al., 1999; Mazoyer et al., 2001). This suggests that the activity observed in these regions is associated with a set of operations that are spontaneously employed when people are mentally unconstrained, rather than a sim-

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ple reflection of random noise. While the specific patterning of recruitment during rest periods varies slightly from study to study, this network most typically includes ventromedial prefrontal cortex (VMPFC) and the anterior cingulate cortex (ACC) (which together will be referred to here as medial prefrontal cortex; MPFC), precuneus, retrosplenial cortex (RSC), and posterior cingulate cortex (PCC) (which together will be referred to here as medial-parietal cortex; MPC), regions of the medial temporal lobe (MTL) (Fig. 1A) and lateral parietal regions such as the supramarginal and angular gyri (Andreasen et al., 1995; Greicius et al., 2004; Buckner et al., 2005).

Of the many purported explanations for the cognitive processes that underlie the activity in the *default network*, perhaps the most dominant is that it arises when people “mindwander,” or engage in thought that is unrelated to the external environment (Mason et al., 2007) and that activity in these regions attenuates when people perform tasks that are attentionally demanding. In other words, these regions “deactivate” when people engage in controlled processing and suspend spontaneous thought processes. According to this account, default activity is an inverse function of task demand, where higher demands reduce activity in the default network because the mental resources used for mindwandering have been reallocated to performing the task (Gusnard and Raichle, 2001; McKiernan et al., 2003, 2006). Our proposal is that this account is incomplete. Specifically, we argue that because the tasks in which this default activity was observed did not recruit the same cognitive processes and cortical regions that are engaged at rest, the differences during task performance were seen as a relative decrease (i.e., a deactivation). When, on the other hand, the task itself demands usage of the same cognitive processes that mediate rest activity, which we propose is the continuous activation of associations, activity in the default network should not decrease during task performance and may, in fact, increase relative to rest periods. This logic will be used here to demonstrate that associative processing is what our brain is most often busy doing.

THE DEFAULT NETWORK OVERLAPS WITH THE NETWORK OF CONTEXTUAL ASSOCIATIONS

In parallel to the notable advancements researchers have made towards elucidating the source of default network activity, relevant findings have emerged in recent studies of the neural correlates of associative processing (Bar and Aminoff, 2003; Bar, 2004; Aminoff et al., 2006). In these studies we concentrated on contextual associations, where seeing a certain stimulus presumably coactivates the cortical representations of other items that are expected to be relevant in the particular situation. For example, seeing a traffic light is a reliable predictor of a road, cars, and pedestrians in a street context, and it is beneficial to activate the representation of these objects in advance in order to facilitate their likely subsequent recognition. Com-

paring the activation elicited by highly associative objects with that elicited by weakly associative objects, in a wide range of paradigms and subject populations, helped define a network of cortical regions that are consistently more active for an increased level of associativity. This network includes the RSC, PCC and precuneus/subparietal sulcus (together MPC), parahippocampal cortex in the MTL, and the MPFC (Fig. 1B) (Bar and Aminoff, 2003; Bar, 2004; Aminoff et al., 2005a,b), which highly overlaps with the medial aspects of the default network.

Put simply, this result indicates that when people see pictures of individual objects that elicit a relatively large number of associations (e.g., a traffic light, a barn, a tennis racket, or a microscope), it activates the same cortical regions that are recruited when people engage in unconstrained thought. This striking overlap between the contextual association network and the default network might seem counterintuitive at first, but we present it here as a manifestation of the degree to which associations provide the principle basis of thought.

The six studies averaged together here to demonstrate this overlap are all studies that focused on associative processing in one way or another, and varied in multiple aspects including the design (blocked and event-related), stimulus material (scenes and isolated single objects), and experimental task (object recognition, classification, and memory encoding). All of these studies show *increased* recruitment of the default network during tasks involving highly associative stimuli, compared with weakly associative stimuli. Specifically, the same medial network implicated as default network was recruited in these studies as a direct function of how much associative processing was required by the task, independent of task difficulty.

The actual experiments are reported elsewhere (Bar and Aminoff, 2003; Kassam et al., 2003; Aminoff et al., 2005a,b) but we describe one here. In this study we compared cortical activation elicited by objects that are highly associated with a certain context (e.g., a microscope) with the activity elicited by objects that are not considered as associative, in that they are not unique to any particular context (e.g., a camera). Each object appeared in isolation. The underlying hypothesis was that associative objects (i.e., objects with strong contextual associations; SCA) would coactivate many representations related also to their associates, whereas weak context objects (i.e., objects with only weak contextual associations; WCA) would result in activation primarily confined to the presented object.

As can be seen in Figure 1B,C, the activity observed in regions of the default network decreases less, and in some cases even increases, when people process objects with many contextual associations relative to when they process objects with few contextual associations. This was true independent of task difficulty (average reaction times for recognizing the objects in both, SCA and WCA, conditions were comparable). In other words, increased associative processing resulted in less deactivation and more activation in the default network, whereas stimuli that elicit little associative processing elicited substantial relative deactivation in the default network. This pattern was especially pronounced in the MPC, MTL, and MPFC. The overlap between the network mediating contextual associations

and the medial default network provides the backbone of our proposal that “default activity” and mindwandering rely heavily on associative processing, and that the MPC, MTL, and MPFC is the underlying neural circuitry.

Taken together, the activity patterns observed in these studies reflect associative processes that might be typical of a “default,” rest state, but that can also be recruited in experimental condi-

tions if the task requires associative processing, which was not the case in the typical studies used to define this default network. The brain might be constantly activating associations, and these associations are either related to information gleaned through the senses, as when we enter a kitchen and identify objects, or they are completely independent of sensory input, as when we mindwander.

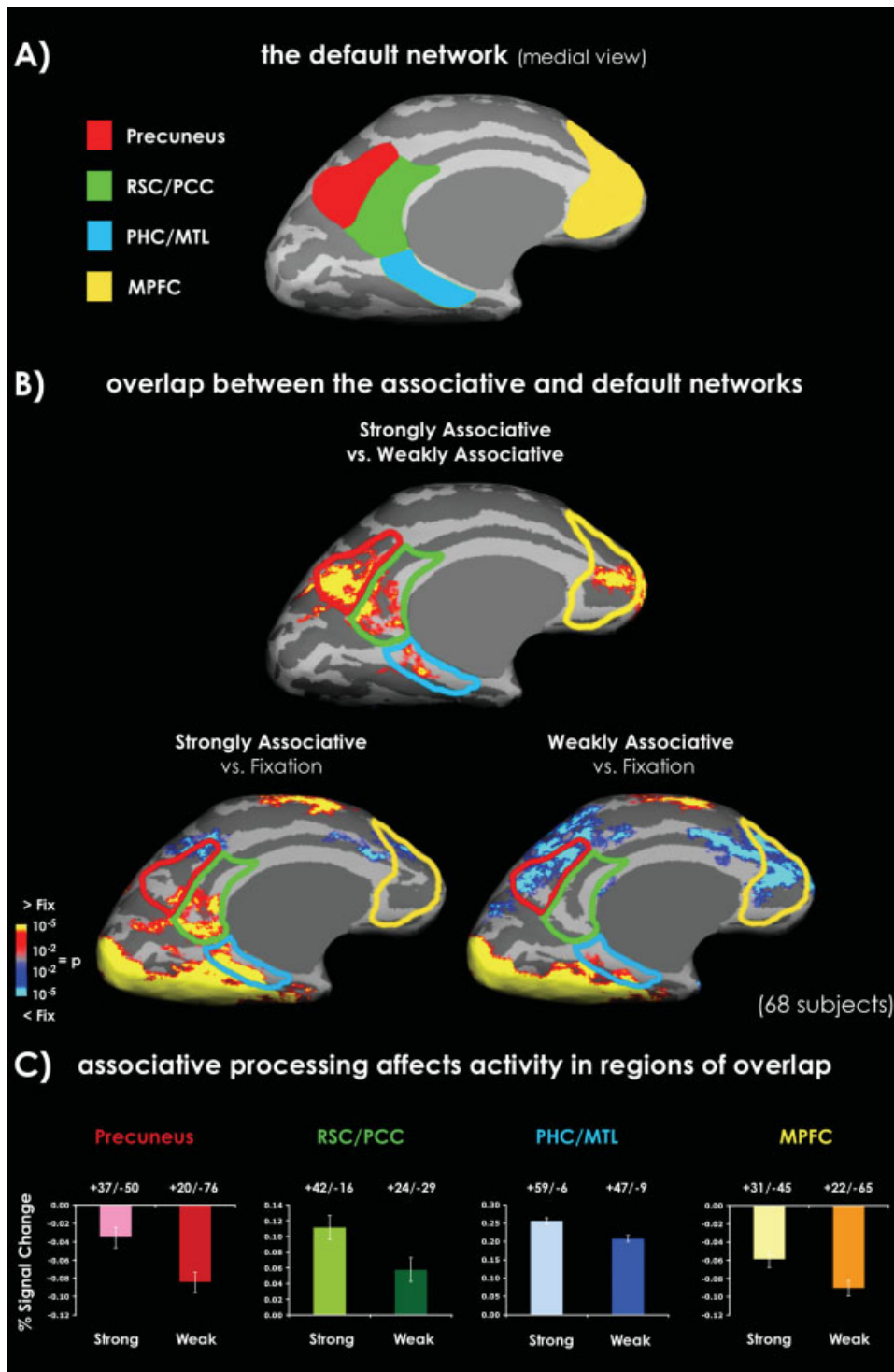


FIGURE 1

Interestingly, the regions of the context and the default network that exhibit the greatest overlap—MPC, structures in the MTL and the MPFC—generally seem to be activated in an exceptionally wide variety of studies. These include studies of navigation and spatial processing (O’Craven and Kanwisher, 2000; Maguire, 2001), error in execution and planning of saccadic eye-movements (Polli et al., 2005), episodic memory (Brewer et al., 1998; Davachi et al., 2003; Ranganath et al., 2004b; Wagner et al., 2005), decision-making (Fleck et al., 2006), emotional processing (Maddock, 1999), self-referential processing (Kelley et al., 2002; Macrae et al., 2004), social interactions (Iacoboni et al., 2004), and mental state attribution (i.e., theory of mind; Saxe and Kanwisher, 2003; Mitchell, 2005; Frith and Frith, 2006). The basic operation that we see as shared by all these diverse processes is associative processing. Navigation processes require associative processing to link landmarks with spatial locations, episodic memories require associations for binding the constituents of an episode, emotional processing and the concomitant heightened arousal they entail are tightly associated with affective memories, and our perception of ourselves and others require associations formed with experience to help interpret the present and anticipate the future. In addition, memory, with its multiple types, seems to be critically dependent on associative mechanisms that link newly acquired information with existing memories. Other functions that are generally believed to be part of the processes that take place during unconstrained thinking, such as problem-solving, planning, and preparing for future events, simulating alternative possibilities, projecting ourselves to possible futures, and replaying past events, also draw heavily on associations with existing knowledge and memory of previous experiences. Taken together, we propose that this network should be seen as emphasizing associative processing, which is crucial for many different functions. In fact, it is hard to imagine another

role that could be assigned to this network that reconciles the fact that processes as different as navigation and emotional processing, for example, elicit activation in the same regions.

DECONSTRUCTING THE OVERLAPPING COMPONENTS

Associative processing has previously been attributed specifically to the MTL (Petrides, 1985; Schacter, 1987; Sakai and Miyashita, 1991; Miyashita, 1993; Shallice et al., 1994; Eichenbaum and Bunsey, 1995; Henke et al., 1999; Eichenbaum, 2000; Suzuki and Eichenbaum, 2000; Murray, 2001; Stark and Squire, 2001; Düzel et al., 2003; Sperling et al., 2003; Ranganath et al., 2004a; Aminoff et al., 2006), in line with our overlap-based proposal. The function of the other parts of the context network (i.e., MPC and mPFC) in associative processing is less extensively studied. As we elaborate later, simple paired-associates, such as those typically used in the studies implicating the MTL in associative processing, are not the only types of associations. Associations can involve numerous elements, and pertain to information that is removed from sensory input by multiple layers of analysis. Different parts within the MTL (e.g., parahippocampal cortex, hippocampus) are likely to be playing somewhat different roles accommodating the various association types. Similarly, the MPC and the MPFC might be involved to varying degrees in the processes related to the different types of associations. Finally, the different types of associations may be further dissected, and more regions are certain to be involved in the processing of additional types of associations. For example, the striatum (Pasupathy and Miller, 2005), the caudate nucleus (Poldrack and Rodriguez, 2004), and even the cerebellum have all been shown to be involved in various

FIGURE 1. (A) Medial view of the typical default network. The labeled regions are those that tend to show deactivation during the experimental task. In other words, these regions are more active during fixation rest than during task performance. These areas include the precuneus and the adjacent subparietal sulcus, the retrosplenial cortex (RSC), and posterior cingulate cortex (PCC) (which we refer to in the text as the MPC), the parahippocampal cortex (PHC) and more broad regions in the medial temporal lobe (MTL), in the anterior cingulate cortex, and the supra-orbital sulcus in the medial prefrontal cortex (MPFC) and in the superior frontal gyrus. Of the areas in this network, the PHC in particular does not always appear in studies of the default network. This seems to depend on factors such as what condition is compared with fixation, the threshold selected for the analysis, and whether the scanning parameters are suited for acquisition of signal from this region. (B) The overlap between associative activation elicited by highly contextual objects and medial regions of the default network. Interestingly, in spite of this striking overlap in the medial surface, there was virtually no overlap between the two networks in lateral regions. Medial activation for the contrast between strongly contextually associative objects (e.g., a tennis racket) and weakly contextual objects (e.g., water bottle) at the top; strongly contextually associative objects vs. fixations/rest condition on the left (associative > fixation in yellow-red, and fixation

> associative in blue); and the contrast between weakly contextual objects and fixation/rest on the right. These statistical maps were derived from averaging together six different experiments, all of which used strongly and weakly contextual objects in various tasks, with a total of 68 different participants. Importantly, the superimposed outlines of default network areas demonstrate the striking overlap between associative processing and resting, task-independent, default processes. (C) The effect of associative processing on fMRI activity in the regions of overlap with the default network, as manifested by percent of signal change. Regions of interest were chosen by the anatomical areas typically found in the default network on the medial surface. These ROIs were labeled based on anatomical landmarks on each individual’s brain. All voxels that were significantly different from baseline (either as a deactivation or an activation, $P < 0.05$) within the structural label were analyzed. The numbers next to each bar indicate the number of voxels that exhibited significantly positive difference from fixation in the specific ROI and condition, and the number of voxels that exhibited a negative difference with fixation (+#/#). Importantly, these graphs demonstrate that in each of these regions, strongly associative objects elicited either stronger positive or less negative activation compared with weakly contextual objects. Furthermore, in each of these ROIs, strongly associative objects activated more positive and fewer negative voxels compared with weakly associative objects.

paradigms related to associative processing. Additional research will be required before a fine distinction of association types and their corresponding neural circuitry will be possible. Of specific interest is the difference between the associative processes mediated by the network discussed here and the associations processed by those other regions. Nevertheless, that the MPFC-MPC-MTL are consistently active during unconstrained thought and with contextual associations evoked by real-world displays indicates that this network has a central role in our everyday mental activity.

While the overlap between the networks was nearly perfect in the medial surface, there was virtually no overlap between context-related activity and default network activity in the lateral surface. This can be used as a reminder that it is not meant to be proposed here that everything cognitive is purely associative. For example, while 7×7 might be solved by the brain using an automatic associative activation, 13×150 requires an actual computation that is likely to involve non-associative components. The areas of the default network that are not shared by the context network presumably mediate such nonassociative aspects of cognitive processing (e.g., computations, transformations, rehearsal, attention, and so on).

The subject of associations and associative processing has been one of the most active directions in neuroscience, neural networks, and cognitive psychology. Together with the voluminous findings, models and theories that this topic has generated there are also ample varieties on the definitions for the underlying terminology. What do we specifically mean when we talk about associations, and which aspects of associative processing might these cortical regions subserve? In the framework proposed here, associations range in the degree of automaticity by which they are activated. At one extreme, associations are simple and unique, and thus analogous to a basic Hebbian association where associated concepts are coactivated when the representation of one of them is triggered (e.g., when a monkey learns that a picture of a blue triangle is always followed by a red circle, or when we anticipate the taste of a lemon before biting from it). Such associations have been the primary subject of research, and have largely been shown to be mediated by region within the MTL (Petrides, 1985; Schacter, 1987; Sakai and Miyashita, 1991; Miyashita, 1993; Shallice et al., 1994; Eichenbaum and Bunsey, 1995; Henke et al., 1999; Eichenbaum, 2000; Suzuki and Eichenbaum, 2000; Murray, 2001; Stark and Squire, 2001; Düzel et al., 2003; Sperling et al., 2003; Ranganath et al., 2004a; Aminoff et al., 2006).

However, not all associations are of the simple stimulus-stimulus, simple form; there are associations that are more deliberative, and their selective co-activation depends on the specifics of the given situation. Consider the following examples: When one sees a flyswatter, there is only one object that is strongly associated with it: a fly. Consequently, seeing a flyswatter sensitizes (i.e., primes) the cortical representation of fly, irrespective of the context in which it is detected. However, an object such as a towel can be associated with many objects and multiple contexts (e.g., a bath or a beach). It would not be efficient to prime all the objects from all these possible contexts automati-

cally. Instead, a multiplexing-like switchboard operation might help take additional contextual information into account, to guide the decision of which context frame is most appropriate (Bar, 2004). Specifically, if the towel seems to be in a bath context, the representation of other objects that are likely to appear in a bath (e.g., a toothbrush), but not in a beach, will be primed selectively. Thus, the activation of this type of associations is often conditional based upon additional aspects of the environment, and is not automatic. Yet more complex types of associations might link the output of different modules performing mental simulations (Barsalou, 1999) and other relatively higher-level operations. For example, suppose you are lying in the scanner, and in between experimental trials, you are planning the dinner you will make yourself when you get home. You will have to take into account what you feel like eating, the ingredients available at home (from what you remember), how much time it takes to prepare the certain dishes (based on your experience), and the time available for this (based on the other plans you have made for the evening). These are numerous pieces of information, represented as clusters of associations (e.g., the state of your refrigerator is one cluster of associations while the sequence of your plans for the evening is another), which are not necessarily all associated with each other until activated by the specific scenario that requires linking them together for the dinner plan. Therefore, complex mental experiences are derived from associations with simpler elements, and these associations are formed through experience based on similarity and frequent co-occurrence in time and space. While the relatively simpler type of associations is mediated by MTL, the more complex ones might be mediated by the PFC (Bunge et al., 2003; Muhammad et al., 2006), and its interaction with the MPC and MTL (Bar, 2004).

EXTERNALLY AND INTERNALLY ORIENTED ASSOCIATIVE PROCESSING

Associations are created with experience, and are used to connect related perceptual, conceptual, and emotional representations. They are multi-modal (e.g., the sound of a train can activate the corresponding image), and they subserve multiple purposes in addition to those detailed previously. For example, associative processing guides the progression of thought. Indeed, during unconstrained thought, we often seem to start from a “seed” and propagate in an associative path (recall the “moon-to-haircut” example from the introduction). It is interesting to consider what guides our switching from one concept to another during this “mindwandering” default state. Is it driven by intentions and specific interest? By strength of associative encoding? By recency of activation? Or by a Google-like activation of a concept as a function of the number of its connections to other concepts? These important questions will have to be addressed by future research on human thinking.

Note that we have not made a clear distinction between associations activated via external stimulation (i.e., perception) and the activation of associations via internally generated

thought. The primary reason for this lack of distinction is because the cognitive brain seems to shift bias between internally and externally related processes seamlessly and frequently, and it is in fact possible that our mind is rarely, if at all, oriented exclusively internally or externally (Gilbert et al., 2005). When we close our eyes and think about the recent vacation in Hawaii, our stream of associative thoughts relies on memory and it is largely internal; when we play a captivating computer game, on the other hand, we might be oriented primarily to the external input; however, even when we are engaged in a simple conversation it is clear that we need to switch often between external processes (e.g., sensory input/output) and internally oriented processes (e.g., access to experience-based knowledge in memory, interpreting the meaning of what we hear and guessing the intentions of the other person). Associations are proposed to mediate both “modes” of orientation. In other words, externally oriented processes (e.g., talking, recognizing objects, playing basketball) rely on associations, and internally oriented processes (e.g., planning, reminiscing, mind-wandering) rely on associations to a similar extent. Associative representations have clear advantages in both modes.

ASSOCIATIONS PROVIDE THE BASIS FOR PREDICTIONS

Associations are proposed to provide the units of thought, but they should not be perceived as the actual content of thought; they merely provide the vehicle for linking related representations. In fact, our proposal is that the primary role of associations and associative activation is to generate predictions, which guide our actions, expectations, plans, and thoughts. To elaborate on this it will be useful to consider our broader theoretical framework: We propose that rather than passively “waiting” to be activated by sensations, the human brain is constantly busy generating predictions that approximate the immediate, directly relevant, future. Building on previous work, this proposal posits that rudimentary information is first extracted rapidly from a perceptual input, and then used to derive analogies linking the input with the most similar representations in memory. The linked stored representations in turn selectively activate the associations that are relevant in the specific context, which provides focused, testable predictions. These predictions facilitate perception and cognition by pre-sensitizing representations all the way downstream to primary cortices. For example, we see a fork, the image of which will never be exactly identical to any in our memory, but we will nevertheless connect it to our existing knowledge about fork and anything that typically comes with it, thereby quickly anticipating many other pieces of information relevant in the immediate situation (e.g., knife, plate, food) and verifying them with the corresponding perceptions. Predictions that involve more complex information, such as those required in social interactions, are a product of additional simulations and forecasting that subsequently guide our decisions and actions. In those cases, the input → memory analogical mapping is

between segments of the complex scenario and segments with which we are already familiar (i.e., frames or schemas context). Such an associations-based predictive framework can explain a wide range of phenomena, from recognition to first impressions and to a host of mental disorders. For example, consider first impressions: when you run into someone new, one of the most natural things to do, consciously or not, is to think of whom this person looks like, based on the representations in memory of the many people you already know. Once a match of any quality has been found, you tend to project the dominant personality traits of the familiar person to this new person. For example, if the familiar person tends to be sloppy, you might think that this new person, who looks somewhat like that familiar person, is also sloppy. This projection of traits can be used as a set of predictions, guiding you, even if often undesirably, in what to expect from the interactions with that person. Such first impressions can be made surprisingly rapidly (Bar et al., 2006b; Willis and Todorov, 2006), based on coarse, minimally analyzed information (Bar et al., 2006b). These initial judgments may then be updated and modified based on the experiences you acquire with that new person. Therefore, beyond simply linking related representations, we propose that the primary function of associations is to trigger the generation of predictions. In the simplest form, the appearance of A creates a prediction that B, which we have learned over experience is highly associated with A, will appear in the immediate environment as well. In a more complex situation, predicting how to get from X to Y will trigger the activation of many associations, all of which mediate the construction of the associative path from X to Y.

In some respects, predictions may be considered a higher level of thought-element than associations; they also provide the basis to the many processes detailed above as occupying the unconstrained mind (e.g., planning, navigating, anticipating the thoughts and actions of others, stereotyping, imagining ourselves in the future, affective forecasting, etc.). The brain seems to be able to extract regularities and familiar patterns from our environment, and associate them with corresponding knowledge in memory to afford the generation of predictions. This idea of predictions as the basis of many, if not most, cognitive processes in the human brain will have to be developed separately because the observations we described here cannot speak to it directly (Bar, 2007). Furthermore, the assignment of the specific role of each of the three main medial regions that comprise the context-default overlap requires more research before we understand the division of labor between them, though some suggestive evidence already exists.

The generation of predictions about the future based on associations with past experiences and memories is somewhat related to Ingvar’s “memory of the future” (Ingvar, 1985). Indeed, the PFC, the MPC, and the MTL have all been reported to show selective activation in recent studies of thinking about the past and the future (Bechara et al., 1994; Okuda et al., 1998; Burgess et al., 2001; Okuda et al., 2003; Dudai and Carruthers, 2005; Addis et al., 2007; Buckner and Carroll, 2007; Szpunar et al., 2007), consistent with the roles we have

assigned here to this network. Also in agreement with the link between memory and predictions are reports showing that patients whose memory of personal events has been compromised are also deficient in predicting personally relevant future events (Klein et al., 2002; Hassabis et al., 2007). Finally, several recent reports show that various parts in the orbital and medial PFC exhibit activation that is tightly related to the generation of predictions (Bar et al., 2006a; Summerfield et al., 2006).

IMPLICATIONS

We have shown that there is a remarkable overlap between the cortical network that mediates the processing of contextual associations and the network of regions recruited during unconstrained thought. We argue that this overlap is the neural indication that associative processing is the principal element of human thinking. Consequently, a compromised association network would result in much more than a simple lack of co-activations, but rather would manifest itself by deficiency in many basic thought and cognitive processes that pervade everyday functioning.

While there are no readily available patients with specific lesions to this focal network, the normal aging process (Lustig et al., 2003; Grady et al., 2006), Alzheimer's disease (Lustig et al., 2003; Buckner et al., 2005), and major depression (Anand et al., 2005) all compromise this cortical network. For example, aging entails morphometric changes (e.g., cortical thinning) in the MTL, MPC, and PFC (Hedden and Gabrieli, 2004; Salat et al., 2004; Lerch et al., 2005; Raz et al., 2005). In parallel to these morphological changes, compared with young adults, older adults show deficits in generating associations from drawings (Puglisi et al., 1987), binding related information (Chalfonte and Johnson, 1996; Naveh-Benjamin, 2000), scene encoding (Gutchess et al., 2005), and learning stimulus-reward associations (Mell et al., 2005). Therefore, the neural correlates of the cognitive decline associated with aging is in agreement with our proposal that these areas mediate continuous associative processing. Interestingly, aging seems to reduce significantly also the frequency of mindwandering (Giambra, 1993), which we propose is mediated by associative processing. In another demonstration of this correlation between structure and cognitive function, Buckner et al. (2005) have shown recently that at least for Alzheimer's disease, the MPC in particular is the first region to atrophy, show metabolic abnormalities and amyloid deposition. Given the connection between these regions and default network activity, they indeed proposed the possibility of "use-it-and-lose-it," whereby the extensive use of these regions makes them lose neuronal volume and connectivity faster than areas that are recruited less frequently. In addition, patterns of default state connectivity are decreased in normal aging, and even more so in Alzheimer's disease (Greicius et al., 2004), as well as with major depression (Anand et al., 2005). This specific effect on connectivity might be informative when considering the exact mechanism of activating associations, predictions, and mindwandering, which requires the integrity of these cross-regional communications.

In summary, older adults, Alzheimer's disease, and depressed patients demonstrate cognitive decline in processes related to associative processing, in parallel to the morphological and functional decline of the overlapping network discussed here, providing support for the role we attribute to this network. The close relation between the cortical network implicated in associative processing and the morphological changes that correspond with age-related and depression-related cognitive decline might provide guidance for therapeutic approaches. For example, it might be possible that engaging in a training program for specific type of associative thinking might possibly postpone the thinning and reduced communication in this network. In depression, one could also imagine that utilizing the associative network in a trainable, different manner than the depressed person is accustomed to do (e.g., dysfunctional ruminating by fixating on a narrow concept) could alleviate the depressive symptoms. Naturally, these optimistic prospects are yet to be examined carefully.

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