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Cognitive Neuroscience: Applied Cognitive Psychology☆

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The Society for Applied Research in Memory and Cognition (SARMAC) was founded in 1994 with a major purpose "to enhance collaboration and co-operation between basic and applied researchers in memory and cognition." Cognitive neuroscience presents opportunities to help actualize the SARMAC vision. The current translational zeitgeist promoted by the National Institutes of Mental Health can be seen as a call for behavioral cognitive psychologists and researchers in cognitive and clinical neuroscience to collaborate to build cumulative knowledge that will advance understanding and treatment of mental disorders. I describe some examples of connections among cognitive psychology, cognitive neuroscience, and clinical neuroscience that are informative from my perspective as a basic researcher in cognitive psychology, and that address (but do not yet answer) some fundamental questions of clinical significance. I also note some challenges of balancing between the goals of understanding and prediction.

Applied science is the art of using scientific knowledge to solve practical problems. Clearly, a better understanding of how the brain works should have far-reaching implications for many practical problems. Cognitive psychology is a major tool for understanding brain function; for example, neuropsychologists and neurologists have long been using methods and concepts from cognitive psychology in their efforts to understand and treat patients with brain damage from disease, strokes, and trauma. The increasing availability of technologies like functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) have tempted many, like myself, who never thought of themselves as interested in the brain, to try to peer inside as minds perceive and reflect. Many young investigators now think of cognitive neuroscience methods as just part of the standard toolkit, like computer-timed stimulus displays and statistical packages. These techniques not only provide additional dependent variables for exploring basic mechanisms of cognition, they increasingly provide useful contact points for behavioral cognitive scientists and cognitive and clinical neuroscientists to share findings and theoretical ideas. Here I describe some of the potential islands of connection among these research domains that I find exciting, in the hope that such examples suggest potential islands of connection in readers' own areas of interest and expertise.

Use of neuroscience methods is increasing rapidly within psychology. Waves of cognitive neuroscience are lapping at the shores of many research domains—learning and memory, economics, marketing, sports performance, lie detection, legal issues of responsibility, etc. For some researchers, cognitive neuroscience may seem less like gently lapping waves and more like a rapacious tsunami. But I want to focus here on what I think are some of the interesting ripples and islands of connection created by interactions among cognitive psychology, cognitive neuroscience, and clinical neuroscience.

Regardless of how we got there, many cognitive psychologists share foundational and catalyzing assumptions. Cognition involves the recruitment of combinations of component processes. Disruptions in these processes result in cognitive problems such as memory deficits, learning disabilities, etc. Cognition and emotion interact (in fact, it may be only for convenience that we separate them) and disruptions in cognition can result in disruptions in emotion and vice versa. Disruptions in cognition, emotion and/or their interaction are core features of a number of clinical problems. These clinical problems are so

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costly to individuals and society that it makes sense to use our taxpayer money to fund National Institutes that support basic and applied research on relevant underlying psychological processes and neural systems.

The Current Zeitgeist

Interestingly, the rise of cognitive neuroscience over the last 25 or so years roughly parallels the rise of the Society for Applied Research in Memory and Cognition (SARMAC) in its central appreciation of applications-relevant research. Psychology is in what might be called a *translational* zeitgeist—a period of increased emphasis on converting knowledge to practical action. Whether experienced as hope or as pressure, whether thought to be long overdue or premature, we bob about in this zeitgeist like a raft in the ocean.

So where are we in this zeitgeist? Steve Peterson and Mike Posner, major leaders in cognitive neuroscience and among its most successful practitioners, are clear about the destination and hopeful about reaching it:

> It has been exciting for us to see the expansion of work on networks of attention over the past 20 years. We now have the opportunity to go from genes to cells, networks, and behavior and to examine how these relationships change from infancy to old age. . ..We are hopeful that the study of attention will continue to provide greater understanding of how control develops typically and in pathology . . .and will provide promising leads for translating basic research into interventions to aid children and families (Peterson & Posner, 2012, p. 85).

Many others are hopeful, of course. But there has also been considerable reflection in the last few years about the slow pace of progress in translation, as highlighted in a recent paper from the lab of another highly successful practitioner of cognitive neuroscience, John Gabrieli:

> Neuroimaging has greatly enhanced the cognitive neuroscience understanding of the human brain and its variation across individuals . . . in both health and disease. Such progress has not yet, however, propelled changes in educational or medical practices that improve people's lives (Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015, p. 11).

Tom Insel (then Director of NIMH), Bruce Cuthbert (then Director of NIMH's Division of Translational Research) and their colleagues suggested some reasons why:

> Diagnostic categories based on clinical consensus fail to align with findings emerging from clinical neuroscience and genetics. The boundaries of these categories have not been predictive of treatment response. And, perhaps most important, these categories, based upon presenting signs and symptoms, may not capture fundamental underlying mechanisms of dysfunction. One consequence has been to slow the development of new treatments targeted to underlying pathophysiological mechanisms (Insel et al., 2010, p. 748).

In fact, Steve Hyman, Director of the National Institute of Mental Health from 1996 to 2001, made the following recent observation:

> Despite high prevalence and enormous unmet medical need, the pharmaceutical industry has recently de-emphasized neuropsychiatric disorders as 'too difficult' a challenge to warrant major investment (Hyman, 2014, p. 220).

And Hyman attributes this trend in part to the absence of reliable biomarkers as diagnostic criteria or treatment targets.

In short, despite the general enthusiasm in recent years about our increasing understanding of brain function, leaders at NIMH, and many scientists in the field, feel like there has been a major logjam in progress converting knowledge to practical action. This logjam is created in part by the practice of grouping clinical problems into diagnostic groups based on the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association, 2013). The argument goes something like this: current DSM-type categories, for example major depressive disorder, mild depression, and bipolar, each include people with a heterogeneous group of symptoms that overlap with the symptoms in other diagnostic categories. It might be useful to deemphasize or ignore DSM category and focus on specific symptoms. In so doing, the goal would be to link individual differences in measures of these symptoms to specific behavioral measures, physiological measures, gene risk scores, brain activity (as expressed in areas or circuits), and life experiences (social, cultural, and environmental factors). The links between symptoms and each of these levels of analysis, and between these levels of analysis, should yield clusters of information that would provide more specific bases for scientific understanding, diagnosis and development of treatments. To this end, they suggest an organization of research around what they call the Research Domain Criteria project (RDoC, Cuthbert, 2014; Sanislow et al., 2010). For example, Research Domains include *Cognitive Systems* (i.e., associated constructs like attention, perception, working memory, declarative memory, language, cognitive control), with the goal of bridging relations between measures of constructs across units of analysis (i.e., genes, molecules, cells, circuits, physiology, behavior, self-reports). The NIMH RDoC initiative is an ambitious, ongoing project to incorporate genetics, imaging, cognitive science, and other levels of information to lay the foundation for diagnosing and treating mental disorders using biological and behavioral measures that are likely to cut across traditional/current diagnostic categories. The long-term goal is "precision medicine"—the ability to diagnose specific problems and target treatments at those problems.

> We recognize that . . . such a new approach is a daunting task. . .. However, NIMH hopes that the scientific and clinical communities will recognize the importance of joining in constructive dialogue on efforts aiming to accelerate the pace of new clinical discoveries and improve clinical outcomes (Insel et al., 2010, p. 750).

What does this mean in practice? For a cognitive neuroscience approach, it would involve several activities: (a) Identify component processes and associated neural/biological correlates of a

construct within a research domain; (b) Examine individual differences in healthy individuals and in patient groups (better yet, across patient groups) with respect to functional and/or structural neural/biological correlates; (c) Predict outcomes in new samples (diagnosis, response to treatment). I don't think this means that any one scientist is expected to do it all—only that accelerating progress will require an explicit effort by individual scientists, groups of scientists, and institutions like NIMH to contribute to bridging these levels and making these connections.

Members of SARMAC or readers of papers in the *Journal of Applied Research in Memory and Cognition* are not likely to need to be convinced that an eye toward applied problems is worthwhile – what I want to highlight is that this is a particularly good time for researchers in cognitive psychology to look for and find connections with other domains – psychiatry, genetics and many domains of neuroscience, to collaborate productively on applied problems related to health.

Attempting to identify components of complex psychological constructs is natural for experimental psychologists and we should expect relevant connections between such work and research in clinical science. As illustrated in the next section, my lab has been informed and encouraged when work from our lab converges with other types of analysis from other labs—for example, structural analyses of brain regions, or studies of disruptions in mechanisms that might relate to clinical symptoms. Such connections suggest more might be accomplished with a more explicit agenda to work in teams, collaborating across units of analysis with an eye to clinical applications.

Targeting Component Processes, Exploring the Self, and Explicating Frontal Cortex

The conceptual model of cognition that guides our lab's work is a midlevel description of component processes of perception and reflection (a Multiple Entry, Modular Memory [MEM] model, e.g., Chun & Johnson, 2011; Johnson, 1992; Johnson & Hirst, 1993, see Figure 1). We have been especially interested in reflective processes—processes such as *refreshing*, *rehearsing*, *retrieving*, *initiating*, etc. We think of these as component processes of the more complex mental activities involved in working memory, long term memory, problem solving, decision-making, etc. In the late 1990s, fMRI seemed like a promising new way to further explore these component processes and we started with what we thought was the "simplest" component process of reflection—*refreshing*. Refreshing is a mental act of directing reflective attention to an active mental representation of something that is not perceptually present. This is a minimal type of reflective attention or a minimal executive function. We've done a number of studies to clarify this theoretical concept of refreshing (e.g., Johnson et al., 2005; Johnson & Johnson, 2009).

In a typical refresh study (see Figure 2A), on each trial, participants might read a word and then within about a half a second they are asked either to read another word, read the same word again, or to think of the just previous word (*refresh* it). Behaviorally, healthy young adults show priming (faster reading) when they read the same word again, and it takes longer for them to refresh the same item than to read a new item (Johnson, Reeder, Raye, & Mitchell, 2002). When young adults do a similar task

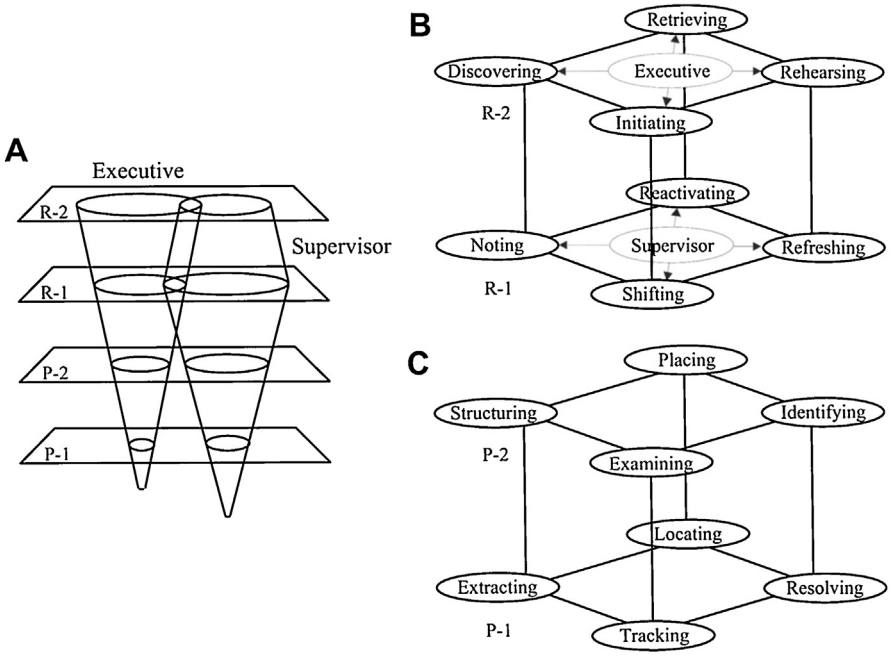

Figure 1. *MEM architecture.* (A) Cones representing executive and supervisor agendas. The width of a cone as it passes through two reflective subsystems (R-2, R-1) and two perceptual subsystems (P-2, and P-1) indicates the degree to which each type of agenda is involved with processing at these levels. (B) Eight reflective component processes associated with R-2 and R-1 levels of processing. (C) Eight perceptual component processes associated with P-2 and P-1 levels of processing. (Adapted with permission from Johnson & Johnson, 2009.).

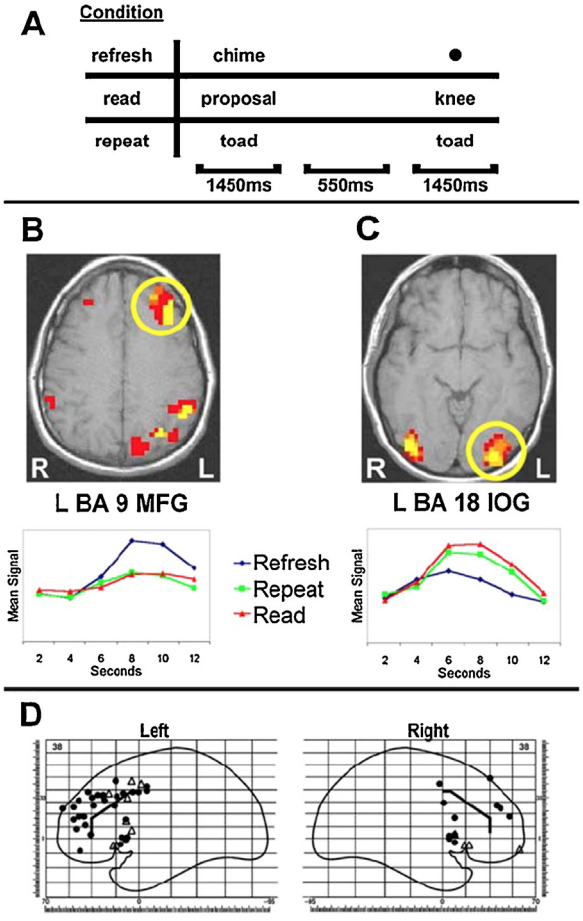

Figure 2. (A) Examples of the *refresh*, *read*, and *repeat* conditions used in Raye et al. (2002) and other studies. (B) Greater activity for refreshing than reading or re-reading word stimuli in left DLPFC. Adapted from Raye et al. (2002). (C) Greater activity for reading or re-reading word stimuli than refreshing in left occipital cortex. Adapted from Raye et al. (2002). (D) Maxima of refresh-related activity plotted for several studies. Circles indicate refreshing a single item, triangles indicate refreshing one of three items. Middle frontal gyrus is above the line, inferior frontal gyrus below. Adapted from Johnson et al. (2005). BA: Brodmann area, IOG: inferior occipital gyrus, MFG: middle frontal gyrus. (Adapted with permission from Johnson & Johnson, 2009).

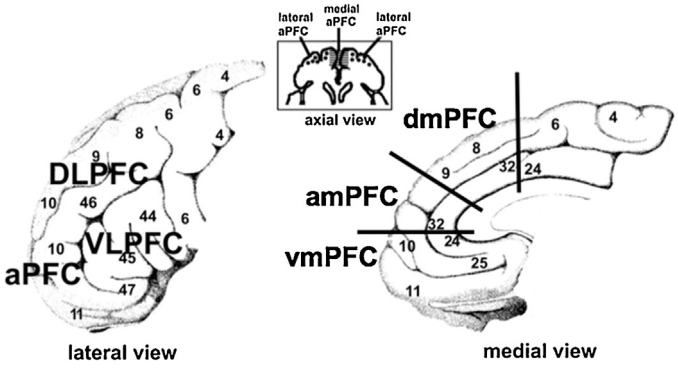

Figure 3. Approximate subregions of prefrontal cortex. Lateral PFC (left): *aPFC* anterior prefrontal cortex, *DLPFC* dorsolateral prefrontal cortex, *VLPFC* ventrolateral prefrontal cortex. Medial PFC (right): *dmPFC* dorsomedial prefrontal cortex; *amPFC* anterior medial prefrontal cortex; vmPFC ventralmedial prefrontal cortex. The numbers are approximate Brodmann Areas (BA) (Adapted with permission from Mitchell & Johnson, 2009).

in an fMRI scanner, we observe left dorsolateral prefrontal cortex (DLPFC) activity (middle frontal gyrus [MFG]) and parietal activity (supramarginal gyrus [SMG]) associated with refreshing (Raye, Johnson, Mitchell, Reeder, & Greene, 2002, see Figure 2B and Figure 3). On a long term recognition memory test, refreshing a word is associated with better long term memory and faster response times than reading the word again (Johnson et al., 2002). Additional studies have distinguished *refreshing* from *rehearsing* (which tends to recruit ventrolateral PFC [VLPFC], see Figure 3) and from *shifting* to/*initiating* a task (which tends to recruit lateral anterior PFC, Raye, Johnson, Mitchell, & Greene, 2007, see Figure 3) and from *noting* whether an item is old or new (which tends to recruit right PFC, Johnson, Raye, Mitchell, Greene, & Anderson, 2003). Applying TMS to left DLPFC slows refreshing in young adults (Miller, Verstynen, Johnson, & D'Esposito, 2008). Also, relative to young adults, older adults show a disproportionate slowing when refreshing relative to reading a new word (Johnson et al., 2002), and they show reduced activity in left DLPFC during refreshing (Johnson, Mitchell, Raye, & Greene, 2004). Across various studies, we've explored refreshing for a number of different types of materials, including visual and auditory words, objects, patterns, people, scenes, and locations: Refreshing consistently is associated with activity in DLPFC, especially MFG, among other prefrontal cortex regions (Johnson et al., 2005, see Figure 2D). When we increase the potential competition by cuing participants to refresh one of three active representations (instead of only a single item), we see increased activity in anterior cingulate cortex (ACC) and in VLPFC; if one of the potentially competing items is emotionally salient, we also see increased activity in orbitofrontal cortex (OFC; Johnson et al., 2005).

Our findings of refresh-related activity in DLPFC are consistent with various findings from other labs using other (and often more complex) paradigms (e.g., the N-back task). We think of refreshing as a minimal executive process that serves functions that others have described as selective attention, task management, manipulation, holding a context, etc. (D'Esposito, Postle, Ballard, & Lease, 1999; MacDonald, Cohen, Stenger, & Carter, 2000; Miller & Cohen, 2001; Petrides, 2000; Smith & Jonides, 1999). That is, all of these functions require *foregrounding* some information so that it has a *competitive advantage* over other information.

Our finding that lateral, anterior PFC is associated with initiating (shifting between agendas, Raye et al., 2007) is consistent with other studies associating activity in this area (sometimes called frontopolar or rostrolateral PFC) with executive functions such as establishing a task set, monitoring and integrating subgoals, hierarchical sequencing, etc. (Badre, 2008; Badre & D'Esposito, 2009; Braver & Bongiolatti, 2002; Christoff & Gabrieli, 2000; Courtney, 2004; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Passingham & Sakai, 2004). These ideas have the common theme of *initiating* a new task or *shifting* between agendas, active representations, or stimulus features.

In sum, refreshing and shifting/initiating are common components of more complex tasks and may account for general similarity in activity in frontal regions found across many

different types of cognitive tasks (e.g., Duncan & Owen, 2000). Nevertheless, subregions of PFC (dorsolateral, ventrolateral, anterior) are involved in differentiable component processes. Variation in location of activity within PFC across studies may reflect differences in the component processes engaged, the type of information acted upon, and/or the amount of interference/competition present.

In theory, thinking in terms of such component processes should help us understand cognitive dysfunction in clinical populations. For example, individuals with schizophrenia show cognitive deficits in working memory and other executive function tasks (Lee & Park, 2005). Meta-analyses (Mizenberg, Laird, Thelen, Carter, & Glahn, 2009) and theoretical reviews (Barch & Sheffield, 2014) of cognitive deficits associated with schizophrenia have emphasized disrupted function of DLPFC. Patients with schizophrenia show deficits in refreshing, and differences from control participants in PFC activity during refresh tasks (Grillon et al., 2005; Grillon, Krebs, Gourevitch, Giersch, & Huron, 2010; Grillon et al., 2013). Thus, refresh deficits may underlie or contribute to differences between patient and control groups in performance in more complex cognitive tasks and in PFC activity. For example, a prominent hypothesis is that schizophrenia is associated with a deficit in the ability to represent goal information in working memory (Barch & Sheffield, 2014); refreshing may be a component process by which goal information is kept active. In effect, refreshing may help privilege a target agenda—that is, keep it alive in the face of potential distraction.

Consistent with this idea, and particularly interesting in the current translational context is a recent meta-analysis by Ramsay and MacDonald (2015) of studies investigating the use cognitive training to improve cognitive function in individuals with schizophrenia. These studies varied in the type of cognitive training and the assessment tasks, but all involved pre-vs. post-training assessment with fMRI and showed generalization to an untrained task. In comparing coordinates from our meta-analysis across refreshing different types of materials (Johnson et al., 2005) and the coordinates from Ramsay and MacDonald's meta-analysis of regions benefiting from cognitive training in individuals with schizophrenia, there was notable similarity in two regions (in Talairach coordinates for Johnson et al. and Ramsay and MacDonald, respectively): Left MFG (−38, 5, 36 vs. −40, −8, 40), Left MFG, superior frontal gyrus [SFG] (−30, 49, 16 vs. −28, 52, 6) that are similar to the dorsolateral and lateral anterior PFC regions associated with *refreshing* and *initiating* (Raye et al., 2007).

In addition to positing specific component processes, the MEM architecture (see Figure 1) offers several ideas about how perception and reflection interact and how their products are discriminated, about the subjective experience of being the origin of mental activity, how two interacting reflective subsystems can give rise to such experiences as thinking about what one is thinking about (e.g., reflecting on reflection) and, more generally, how various aspects of a sense of self are generated, monitored and/or represented (Johnson, 1991, 1997; Johnson & Hirst, 1993; Johnson & Raye, 1981; Johnson & Reeder, 1997). Cumulative evidence from many labs indicates that medial frontal cortex (mPFC, including cingulate cortex, see Figure 3) is involved in a number of aspects of self (control, agency/origin, identity/ownership, value/affiliation). Furthermore, meta-analyses indicate that more dorsal mPFC (roughly, $z > 20$) is associated with cognitive tasks (especially conflict monitoring), a mid-section (sometimes referred to as anterior mPFC) is associated with affective, social, and self-referential tasks), and a still more ventral section (roughly, $z < 0$; sometimes referred to as ventral medial, orbital medial or subgenual medial PFC) is associated with reward processing (e.g., Amodio & Frith, 2006; Bush, Luu, & Posner, 2000).

For example, one of the most reliable findings in fMRI studies of cognition is that dorsomedial PFC (especially ACC) activity increases with increases in task complexity and the requirement for cognitive control (Botvinick, Cohen, & Carter, 2004), as in the example described above where ACC activity increased when potential competition was introduced in a refresh task (Johnson et al., 2005). The idea that DLPFC and ACC are major elements of a control network is well established (Botvinick et al., 2004). Although the following discussion focuses on mPFC, specific psychological functions clearly reside in interactions between mPFC and other brain areas.

According to the source monitoring framework (Johnson, Hashtroudi, & Lindsay, 1993; Johnson & Raye, 1981; Mitchell & Johnson, 2009), information about cognitive operations carried out provides one type of cue that the self is/was the origin of an experience (e.g., as in reality monitoring). Assuming mPFC reflects some aspects of control, records of mPFC activity should be associated with information about cognitive operations performed, which can serve as a cue to the origin of remembered information. There is a fascinating line of work, much from Jon Simons' lab, that finds greater anterior mPFC activity when participants are engaged in reality monitoring tasks compared to control tasks including other types of source monitoring tasks (Kensinger & Schacter, 2006; Simons, Davis, Gilbert, Frith, & Burgess, 2006; Simons, Gilbert, Owen, Fletcher, & Burgess, 2005a; Simons, Henson, Gilbert, & Fletcher, 2008; Simons, Owen, Fletcher, & Burgess, 2005b; Turner, Simons, Gilbert, Frith, & Burgess, 2008; Vinogradov et al., 2006). For example, one study found greater anterior mPFC activity when participants remember performed vs. imagined actions (Brandt, Bergstrom, Buda, Henson, & Simons, 2014).

Schizophrenia is clinically associated with reality monitoring deficits such as hallucinations and delusions. Keefe, Arnold, Bayen, McEvoy, and Wilson (2002) found poorer performance in patients with schizophrenia in a laboratory reality monitoring task. Furthermore, Vinogradov, Luks, Schulman, and Simpson (2008) found a reality monitoring deficit in patients with schizophrenia that was associated with reduced activity in anterior mPFC. Converging evidence about the importance of anterior mPFC for reality monitoring comes from a study of cognitive training of patients with schizophrenia (Subramaniam et al., 2012). After 16 weeks of cognitive training, improved performance on a reality monitoring task of patients was correlated with anterior mPFC activity.

Especially provocative is evidence about structural features of mPFC that have implications for reality monitoring. An area of mPFC, the paracingulate sulcus (PCS), is less prominent or

more likely to be absent (especially in the left hemisphere) in patients with schizophrenia relative to controls (Yucel et al., 2002), and amount of reduction is associated with the probability of hallucinations (Garrison, Fernyhough, McCarthy-Jones, Haggard & Simons, 2015). Equally fascinating, this is an area that varies quite a bit in the general population. Healthy volunteers can be categorized as having a PCS in both hemispheres, on the left only, on the right only, or absent in both hemispheres. Buda, Fornito, Bergstrom, and Simons (2011) found poorer reality monitoring performance in individuals lacking a PCS in both hemispheres. The anterior mPFC activity found in Brandt et al.'s (2014) performed vs. imagined reality monitoring study was near the average PCS location of the participants. (Such findings prompt wondering about one's own PCS.)

Activity in mPFC also has been associated with explicit self-referential processing, that is, taking oneself as the object of attention. For example, anterior mPFC is more active when people make judgments about whether an adjective such as "honest" or "irritable" describes them than when they decide if it describes another person such as George Bush (Amodio & Frith, 2006; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). Activity in mPFC is also observed during "rest" (i.e., when participants have no particular task in the scanner) and mPFC typically deactivates during cognitive tasks that aren't self-referential. The network of activity during "rest" is quite similar across people and is often referred to as the *default* network—with mPFC as one of its primary hub nodes (Greicius, Grasnow, Reiss, & Menon, 2003; Raichle et al., 2001). (I do wonder if the investigators who decided "rest" should be called "default" have too much time on their hands.) Together this suggests that activity in mPFC during "rest" may signal that people are thinking about themselves.

A series of studies in our lab was based on the idea that the self is composed of more than traits: for example, we are also about our hopes and aspirations and duties and obligations. Our initial thought was that during "rest" people are likely to be thinking about what they would like to be doing – hopes and aspirations- or what they have to do – duties and obligations. (Every experimental question is a projective test. . .) So that's what we cued participants to do while in the scanner (Johnson et al., 2006). The non-self reflective control task was thinking about more concrete items such as "a truck load of watermelons," or the "Mona Lisa." We found a typical pattern of greater mPFC activity in self-referential than non-self referential conditions (Figure 4). In a dorsal mPFC region, there was no difference between hopes and duties (Figure 4A). But, a ventral mPFC region showed an interesting dissociation—more activity for hopes than duties (Figure 4B).

This dissociation between dorsal and ventral mPFC was intriguing and we replicated it several times (Johnson, Nolen-Hoeksema, Mitchell, & Levin, 2009; Mitchell. et al., 2009). In one study (Johnson et al., 2009), we also included participants meeting criteria for major depressive disorder (MDD). The depressed group did not differ in activity from healthy controls in either mPFC region. That is, when specifically prompted to think about hopes and duties, the depressed group looked like control participants in both dorsal and ventral mPFC regions. In

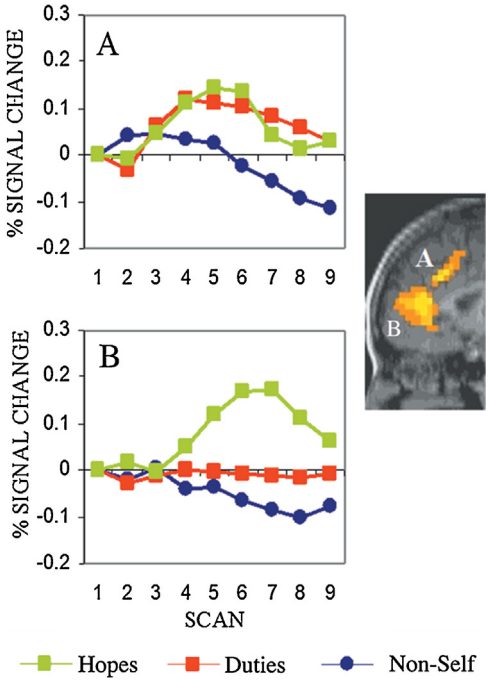

Figure 4. Areas of anterior cingulate and medial frontal gyrus identified: a dorsal mPFC area ([A] −2, 24, 31) showed Hopes = Duties > Non-Self and a more ventral mPFC area ([B] 2,39, −1) showed Hopes > Duties > Non-Self. (Adapted with permission from Johnson et al., 2006).

a second study, the cues were less directive about the valence of the thoughts participants should be having. In this second study, we compared: (a) prompts used in the clinical literature on depression and rumination that had been previously shown to be likely to induce self-evaluation (e.g., *think about who you strive to be, why things turn out as they do*), and (b) prompts that focus participants' attention on their current state (e.g. *think about your current physical sensations, how alert you feel*), and again (c) the non-self-referential prompts (e.g., *imagine a truckload of watermelons*). Both a and b direct participants' attention to the self, and neither direct attention specifically to positive or negative aspects of the self. In this case, we found that the depressed group did not differ from the control group in the current state condition, but showed less activity than the control group in both anterior and ventral mPFC in the self-evaluation condition (see Figure 5). These findings are consistent with behavioral findings that depressed individuals are less likely to have positively-valenced (e.g., hopes) thoughts when prompted to engage in self-evaluation with prompts that are ambiguous in valence. Notably, the MDD participants evidently were not simply less likely to self-reflect; they showed greater mPFC activity than controls in the non-self-referential control condition, suggesting they were less likely to disengage from self-reflective processing when it was not task relevant. Also intriguing is that the ventral mPFC area showing a deficit associated with MDD in Johnson et al. (2009) was very near a region associated with the valuation of goods (money, trinkets, snacks; Chib, Rangel, Shimojo, & O'Doherty, 2009). However, it should be noted that different situations may recruit different brain networks during

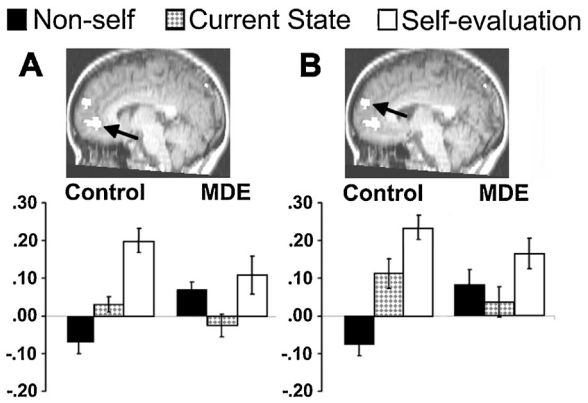

Figure 5. Bar graphs show the mean percent change in bold signal value for Control and major depressive disorder (MDE) groups. Two areas of anterior medial cortex (A and B) showing Control > MDE in the Self-evaluation condition and MDE > Control in the Non-self condition, with no difference in the Current state condition. (Adapted from Johnson et al., 2009).

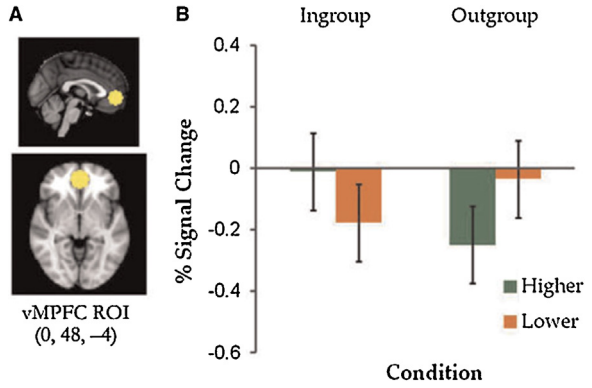

Figure 6. (A) ventral mPFC region of interest (ROI: 0, 48, −4) derived from a self-referent > other-referent contrast in an independent trait descriptiveness rating task and (B) mean percent signal change in the ventral mPFC ROI as a function of condition (Ingroup or Outgroup) and post-vs. pre-ownership preference change (higher or lower). Error bars represent 95% within-subject confidence intervals. (Adapted with permission from Kim & Johnson, 2015).

evaluation (e.g., social vs. non-social contexts, Van Den Bos, McClure, Harris, Fiske, & Cohen, 2007).

Here is another thought-provoking fact: A recent study by Treadway et al. (2015) found that decreased cortical thickness in ventral mPFC was associated with number of prior depressive episodes. It remains to be determined if cortical thinness in this area is a risk factor for depression or a consequence. In either case, if cortical thinness is related to the ease of recruiting this region, that would explain why more specific cues are required for depressed individuals to do so.

It would be tempting to conclude that ventral mPFC simply is associated with positive value—as suggested by the findings of Chib et al. (2009). However a recent study by Kyungmi Kim in our lab (Kim & Johnson, 2015) suggests this may not be quite the way to characterize the function of this region of mPFC. This study was part of a series of studies on the "mere ownership" effect. Our "selves" are not only made up of our traits and our hopes and duties. We are also our "stuff"—the objects we possess. In Kim's studies of the ownership effect, participants imagined owning some objects and imagined someone else owning other objects. She compared change in preference ratings for the objects (from before ownership assignment to after) and obtained a typical mere ownership effect—that is, we like *our* stuff better (my meaningful souvenirs—your junk). She also found that this increase in preference for "my" objects was associated with activity in ventral mPFC during the assignment of ownership (Kim & Johnson, 2012). One possibility is that ventral mPFC activity reflects a positivity that arises from associating objects with the self: Anything associated with me is good—my traits, my ideas, my stuff.

She tested this idea with another experiment (Kim & Johnson, 2015): Prior to scanning, participants rated their preference for objects. During scanning, they were asked to imagine owning all of the objects, each of which was "given" to them by either an ingroup member who currently owned and highly valued the object or an outgroup member. They later gave preference ratings again. She found that greater ventral mPFC activity during ownership assignment was associated with both *increased* later preference for objects from the ingroup member, and *decreased* later preference for objects from the outgroup member (see Figure 6). This pattern of findings is not consistent with the idea that activity in this particular area of ventral mPFC generally reflects positivity. Rather, the pattern of results is consistent the idea that it more likely reflects personal significance. It is personally significant to associate with (i.e., like) objects from the ingroup and to dissociate with (i.e., dislike) objects from the outgroup.

In short, different regions of mPFC are observed in various studies of self-related processing. Like the different areas of the lateral PFC that show up in different tasks as discussed above, different areas of the medial PFC are likely to underlie different phenomena and/or processes. Activity associated with complex cognitive processing (e.g., involving detecting and controlling competition) tends to involve more dorsal regions; areas associated with generating and/or monitoring cognitive operations, and the areas associated with positivity and/or with personal significance tend to be more ventral and themselves may be dissociable (i.e., in anterior mPFC or ventral mPFC regions). Further explicating functional differences among mPFC regions is an important goal. Given the likely importance of characteristics of self-related processing in clinical populations, sorting these out should give us clearer understanding of how different symptoms in clinical populations (e.g., deficits in assignment of agency; loss of positive affect) and individual differences in non-clinical populations may be associated with differences in the structure and/or function of these areas. That is, particular behavioral symptoms may cut across typical clinical diagnostic categories or vary in expression within a category, and these may be tied to structural and/or functional differences in subregions of mPFC.

Predictive Models

The translational zeitgeist includes another trend that is taking off in cognitive neuroscience (but that is not specific to cognitive neuroscience)—the effort to create predictive models. My understanding of and experience with this approach is

limited, but I want to mention it because it is quite different and potentially complementary to experimental manipulation of task characteristics to identify component processes and/or dissociate functional subregions of cortex, and the predictive models approach may spark ideas in researchers interested in applications. A recent article by Gabrieli et al. (2015) is an excellent introduction to this approach. Briefly, there are several phases in creating predictive models. (1) A discovery phase of exploring and evaluating associations (e.g., between neuromarkers and behavioral outcomes), using only a portion of the available data. (2) A model building phase, where potentially interesting variables are used to build, or "train," a model. In order to determine good model parameters for the data at hand, cross-validation is used to separate data into training and test sets. Models are built using training data and tested on test data. Assuming success, all data are used to build a prediction model, using the most appropriate model parameters. (3) A generalization phase in which the model built via cross-validation is applied to a new data set. The new data are then used to update the model.

This approach can be used as an hypothesis free, data-mining approach for relating biomarkers (brain data, genetic data, etc.) to specific symptoms and treatment outcomes. But the approach is not limited to neuro data. It is just as applicable to behavioral data, such as obtained in patient histories, clinical observation, or subjective reports. For example, machine-learning models have been generated from subject-report data to predict persistence and severity of major depressive disorder (Kessler et al., 2016), and clinical response to an antidepressant (Chekroud et al., 2016). The confidence that clinicians currently can have in predicting depression course for individuals and/or outcome efficacy when prescribing particular pharmacological treatments to particular patients for depression is surprisingly limited. The interest in using rigorous data mining to discover systematic relations among variables or to discover useful prediction algorithms (even if we don't understand them) is another reflection of the current translational desire to find new ways to move toward applications faster.

These data mining approaches depend on large data sets and, of course, the quality of the discoveries will depend on the amount and comparability across collection sites of the data being used. This "amount" issue is one argument for sharing data across labs, public data repositories, etc. For example, the International Committee of Medical Journal Editors (2016) recently invited comment on a plan to require public sharing of deidentified patient data within 6 months for any paper published in the member journals. The "comparability" issue to accrue large data sets is tougher—it argues for greater standardization of the variables collected and entered about individuals. However, standardizing research practices potentially reduces the chances of discovering relationships among variables not in the standardized set.

Contemplating the challenges of obtaining agreement to standardize practice among researchers reminds me of a discussion organized by Larry Squire at the 2nd annual meeting of the Memory Disorders Research Society in 1990. The issue was the potential value of greater standardization across labs in the neuropsychology tests investigators report to characterize patients with brain damage. The idea was that speeding up our understanding of brain function would come from being able to better compare and cumulate evidence across publications, especially because patients with similar brain damage are relatively rare. There was a surprisingly spirited discussion (at least surprising to me as a relative novice in cognitive neuroscience at the time). The objections ranged from the idea that it is counterproductive to specify neuropsychological tests if we don't know what the best tests are, to the concern that if we adopt standards and reviewers of submitted articles start to use them, it will disadvantage researchers who have unpublished studies in the pipeline that didn't collect all the recommended measures. No agreement was reached. Nevertheless, researchers increasingly appreciate the value of common reference points (e.g., neuropsychological tests, brain regions reported for fMRI data) for aggregating information across studies (e.g., in meta-analyses).

Prediction and Understanding

Moving forward, we need to remind ourselves occasionally that prediction and understanding are different, as suggested by these thoughtful observations:

> Individual differences in neural systems associated with the response to treatment are not necessarily the ones most affected by a disorder. . .if therapy helps a patient learn to regulate thoughts or emotions, the neuromarkers associated with treatment response may be in neural networks that support such learning rather than in networks related to the etiology or progression of the disorder (Gabrieli et al., 2015).

And,

> the relatively modest correlations with functional outcome. . .measures [suggests] that assessments of more specific component processes may come at the cost of reduced relationships to clinical outcomes of interest. . ..more complex multicomponent measures are more likely to be strongly related to performing complex tasks (as required in many forms of employment and in managing independent living) than focal measures of a single process (Gold et al., 2012, p. 151).

Changes in cognitive interpretation or habits may reduce clinical symptoms, which could mean that an underlying "disorder" (e.g., unusually responsive amygdala; structurally thin ventral mPFC) remains untreated and people are simply coping better. Alternatively, it could mean that a better balance was achieved between the interacting processes that yield our complex cognitive/emotional experience. The fact that a measureable deficit in an isolated cognitive component may be a poor predictor of daily functioning makes the science of understanding hard but is perhaps encouraging evidence of the human talent for finding ways of coping.

Summary

In considering interactions among cognitive psychology, cognitive neuroscience and clinical neuroscience, two major trends of the translational zeitgeist we inhabit are efforts to: (a)

analytically/experimentally identify component processes and connect them across levels of analysis (cognitive/behavioral, brain region/network, genetic, social/cultural) and (b) exploit powerful data mining statistical tools to discover and predict relations among variables. Despite the enthusiasm of those already involved in these approaches, even some of the most accomplished researchers note the limits of what can be claimed so far and the challenge of making progress. There is plenty of room for new energy and ideas about how to connect theoretical ideas about cognition and emotion with behavior, social/cultural context, brain circuits, and genes. In the next few years we should see many exciting ripples, and challenging crosscurrents, reflecting an ongoing synergy and tension between understanding and application. While the associated theoretical and empirical research activity should deepen knowledge arising from cognitive psychology, cognitive neuroscience, and clinical neuroscience, hopefully the big winners will be patients.

Conflict of Interest Statement

The author declares no conflict of interest, financial or personal.

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