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ATTENTION, VARIABILITY, AND BIOMARKERS IN ALZHEIMER'S DISEASE

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Jacoby's work has been remarkably influential not only in its depth within the area of memory but in linking important principles across diverse fields. For example, Jacoby has influenced our understanding of work in categorization, social psychology, aging, neuropsychology, and attention. The present chapter also focuses on the importance of cross-fertilization. Here, we will emphasize the intersection of attention and memory in understanding healthy aging and early stage Alzheimer's disease (AD). Our goal is to bring to fore some relatively novel approaches to understanding the cognitive changes and underlying neural mechanisms across these different populations.

The outline of the chapter is as follows: First, we will discuss early stage Alzheimer's disease, its prevalence, and what cognitive psychologists might bring to the table in understanding and hopefully helping to remediate this devastating disease. Second, we will discuss some work demonstrating that there is accumulating evidence that AD is not simply a disease of memory systems but also influences attentional control systems. Here we will focus both on error rates in attentional tasks, and reaction time distributional analyses. Third, we will provide a brief introduction of the encouraging work identifying biomarkers that appear to accumulate years (and possibly decades) before the development of overt AD symptoms. Finally, we will provide some recent evidence that suggests there is a relationship amongst these biomarkers and breakdowns in the aforementioned attentional control systems.

Healthy Aging and Alzheimer's Disease

Hopefully, we are all cognizant of the impending health disaster produced by AD that is on the horizon. The basic problem is that through medical advances life

expectancy is increasing. For example in 1950 the U.S. life expectancy was approximately 68 years, whereas today it is 78.7 years. This is good isn't it? The problem is that although we can keep the heart pumping into advanced age, there are breakdowns in other systems as one ages. Here we focus on the aging neural system. In particular, there is a strong relationship between age and the likelihood of developing AD. For example, after the age of 65, the prevalence of AD is about 10%, while after the age of 85 the prevalence increases dramatically to nearly 50% (Evans et al., 1989; Kukull et al., 2002; but see Qiu, von Strauss, Bäckman, Winblad, & Fratiglioni, 2013, for recent more positive trends). The physical, emotional and financial drain on families of AD patients is extraordinary. The estimated financial cost of AD in the United States in 2013 is $203 billion, and the projected cost of AD in year 2050 is $1.2 trillion (Alzheimer's Association, 2013). In part, because AD is considered a disease of cognition, and a natural consequence of aging, there has been less urgency in funding AD research, compared to other diseases. For example, research in cancer, heart disease, diabetes, etc. has produced considerable decreases in mortality rates from 2000 to 2010, but deaths due to AD have risen 68% during this same period of time.

There is now accumulating evidence that AD is developing in the brain long before dementia has developed. A powerful demonstration of this is reflected in a study by Morris et al. (2004). In this study, neuropathologists examined 97 brains of individuals from 7 different Alzheimer's Disease Research Centers across the United States who were clearly not demented according to the very sensitive Clinical Dementia Rating Scale (Morris, 1993). Remarkably, about one-third of these non-demented individuals had sufficient neuropathology building up in their brains such that upon close inspection, a neuropathologist would make the diagnosis of AD. This observation has two important consequences. First, it is likely that when studying "healthy aging" the older adult sample is indeed likely to include some individuals who are starting to show subtle cognitive slippage due to the disease process. It is possible that these individuals have sufficient cognitive reserve or other factors that mitigate the cognitive consequences of the disease (see for example, Stern, 2002). Thus, one must be careful in making inferences about "healthy" cognitive aging (Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003; Sliwinski, Lipton, Buschke, & Stewart, 1996). Second, and most importantly for this chapter, if one could somehow measure these subtle cognitive changes and relate these to AD-related biomarkers, it is at least possible that one might intervene with therapy before the ravages of the disease have taken place.

Alzheimer's Disease and the Memory Myopia

AD is still considered primarily a disease of memory, and there is no doubt that memory measures are useful in diagnosing the disease. However, the emphasis on memory may be too narrow, and potentially counterproductive. For example, the

focus on memory tends to orient researchers to specific neural structures, e.g., the medial temporal lobes, in developing models of disease pathology. Indeed, recent developments in neuroimaging AD-related pathology, which allow in vivo measures of amyloid burden, have indicated that there is widespread involvement of multiple systems including frontal areas, and medial parietal areas. This has led to a more systems-wide approach in thinking about AD-related neuropathology (see Buckner, Andrews-Hanna, & Schacter, 2008)

Cognitive psychologists have long considered the important role of attention in the formation and retrieval of memories. Of course, all students of memory know of Craik and colleagues work on the depth of processing framework (e.g., Craik & Lockhart, 1972), in which the emphasis in memory formation is viewed as a consequence of attentional/perceptional operations. The role of attention is also central to Jacoby's (1991) development of process dissociation procedures to dissociation recollection vs familiarity-based processes. Importantly, Jacoby (1999) has tied his views on recollection to attentional systems. Indeed, the controlled vs automatic processing distinction is critical to many of the process dissociation manipulations that Jacoby has developed. Interestingly, Jacoby and others have shown that one can mimic older adults' performance by simply putting younger adults under an attentional load (see, e.g., Balota, Burgess, Cortese, & Adams, 2002; Castel & Craik, 2003; Jacoby, 1999). Regarding the memory myopia in AD research, such patterns at the very least point to the importance of considering the contribution of attentional systems to the observed memory deficit in AD.

McCabe, Roediger, McDaniel, Balota, and Hambrick (2010) reported a study that highlights the relationship between attention and memory in healthy aging.
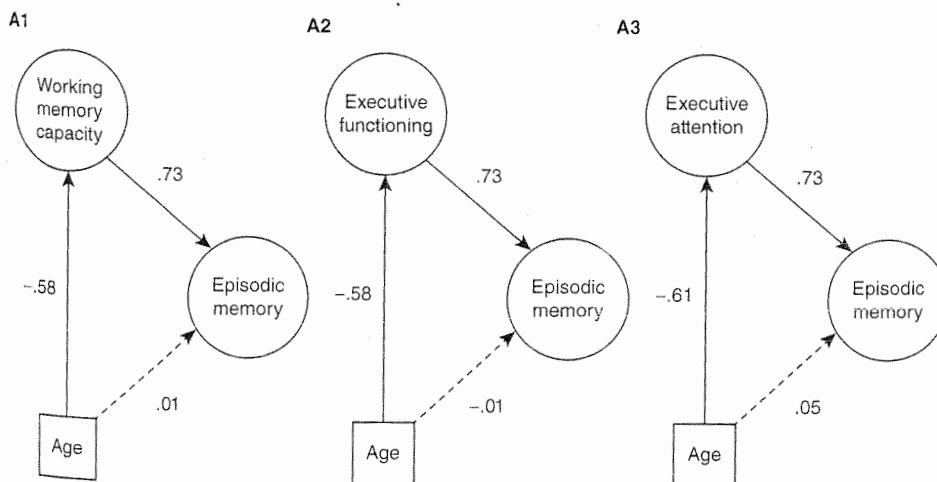

FIGURE 18.1 Structural equation models examining the relation between age and episodic memory with either working memory capacity (A1), executive functioning (A2), or executive attention (A3) as the mediator. Solid lines represent significant correlations ($p < .01$), dotted lines represent nonsignificant correlations.

Specifically, they measured a wide variety of cognitive tasks in participants aged 20 to 90. One of the issues addressed in their paper is whether there is a direct relationship between age and episodic memory loss or whether this relationship was mediated by other variables. McCabe et al. found through structural equation modeling that the relationship between age and episodic memory was indeed totally mediated by either (a) a latent variable reflecting three working memory measures or (b) a set of three attentional control measures, which had minimal episodic memory demands. Indeed, because of the similarity of these two latent variables and the similarity in the excellent fit of the models, McCabe et al. decided it was most parsimonious to combine these into a single latent variable they referred to as executive attention, which totally accommodated the relation between age and memory (see Figure 18.1). Of course, this pattern would not be surprising to a student of Jacoby, since he has long appreciated the critical relationship between attention and episodic memory, which, as noted, is central to his process dissociation perspective.

The Myth of Process Purity in Neuropsychological Tasks

In most neuropsychological studies of cognitive performance across different populations, there is an emphasis on standardized neuropsychological tests to discriminate control groups from the targeted populations along some cognitive/perceptual/motor dimension. For example, in the AD research community, one task that is heavily relied upon is the Logical Memory task (Wechsler & Stone, 1973), in which participants are required to remember a paragraph immediately and after a brief (15 to 30 minute) delay. Indeed, this task is a powerful marker for AD. However, one might ask whether this task is a process pure measure of episodic memory or is also reflective of other cognitive operations such as attention in understanding (encoding) and retrieving the paragraph. Here, one is reminded of the utility of task analysis (see Crowder, 1976), and again the important extension in Jacoby's process dissociation (PDP) approach. Jacoby has emphasized that no task is process pure, but one should attempt to tease apart different processes embedded within the task. As noted, most often in this procedure, one is teasing apart attention-demanding recollective processes from more automatic familiarity processes. Because familiarity processes are more involved in recognition tasks, it is likely that the free recall demands of the Logical Memory task are much more dependent on attention-demanding recollective processes.

One might argue here that if indeed attention is so important in the memory breakdowns in AD, wouldn't one simply rely on psychometric tests that primarily measure attention? These tasks should show quite large deficits. Indeed, we would argue that they do. In fact, recent meta-analyses have emphasized the importance of attentional mechanisms in predicting sensitivity to biomarkers and predicting progression in longitudinal designs (e.g., Small, Rosnick, Fratiglioni, & Bäckman, 2004; Twamley, Ropacki, & Bondi, 2006). Twamley et al. noted:

[a]ttention, although not commonly assessed as learning and memory in preclinical AD, is even more consistently associated with later development of AD. Only 10% of the longitudinal case-control studies measure attention, but of those 100% found that attention performance discriminated cases vs controls.

(p. 709)

One also needs to keep in mind here differences in the reliability of various psychometric measures. Because memory measures are simple point estimates (i.e., how many words or idea units recalled in the Logical Memory task) they have an intrinsic benefit compared to attention measures that sometimes involve difference scores (e.g., the difference between Trials A and Trials B in speeded tasks). The bottom line here is that if Task A is less reliable than Task B, then Task B will show better discrimination. In this light, it is incumbent upon researchers to develop more reliable measures of attentional control systems.

Attention, Aging and AD

Over the past two decades we and many others have been accumulating evidence that indeed attentional control systems are compromised in early stage AD (see reviews by Faust & Balota, 2007; Perry & Hodges, 1999). As noted above, breakdowns in attentional control systems have already been well established in healthy aging (see, e.g., work by Hasher, Zacks, & May, 1999), and the relevance of these attentional breakdowns and episodic memory have also been established. In this section, we will briefly review some of this evidence regarding changes in early stage AD.

In an early study, Spieler, Balota, and Faust (1996) investigated the gold standard measure of attention, the Stroop task, in healthy aging and early stage AD individuals. This project was in part motivated to better understand changes in attentional control systems in these populations. A previous paper by Lindsay and Jacoby (1994) in part motivated this project because they developed a PDP procedure to decouple the more automatic contributions of the word dimension from the more attention-demanding contributions of the color dimension to Stroop color-naming performance. Because of space limitations, we will focus on two simple findings from this study. First, the study was important because it provided some evidence on the utility of examining the shape of response time (RT) distributions within participants instead of simply the mean or median response latency for that participant/condition. As we will see later, this has become a relatively central aspect of our research endeavor. Second, the major discriminator between healthy older adults and early stage AD individuals was not the size of the Stroop effect in mean reaction times, but rather the errors in the Stroop task. (AD individuals did produce larger overall Stroop RT effects, but these effects were not particularly large after controlling for differences in overall response latency, see Faust, Balota, Spieler, & Ferraro, 1999.) The errors were more informative. Of

course, even in healthy high-functioning young adults, individuals sometimes make an error in Stroop performance and say the word instead of the color name. These errors were particularly powerful in discriminating healthy aging from early stage AD. This finding nicely complemented other tasks that we were exploring at the time wherein early stage AD individuals have an increased likelihood of intruding a prepotent dimension in the face of the task relevant dimension (e.g., Balota & Ferraro, 1993; Faust et al., 1999). The simple interpretation of this finding is that healthy older adults have sufficient control to produce a response based on task demands, whereas individuals in the earliest stage of AD are actually driven by the prepotent dimension and hence produce errors.

Is there any direct link between attention control used in Stroop performance and episodic memory performance, one of the major diagnostic markers for early stage AD? Here we turn to an interesting finding in aging and AD research related to intruding related words during episodic recall tasks. Specifically, one finds that healthy older adults and individuals with early stage AD are more likely to produce errors in the Deese, Roediger and McDermott (DRM) paradigm (Roediger & McDermott, 1995). In this paradigm, lists of words related to a critical non-presented word are presented for later recall. Balota et al. (1999) and Watson, Balota, & Sergent-Marshall (2001) have shown that there is a relative increase in the false recall of non-presented critical words compared to presented words as a function of both age and AD status. They interpreted this pattern as reflecting a problem in controlling the powerful familiarity signal provided by the convergence of the words on the non-presented critical item. Further, they argued that this has at least some face value in relation to controlling the prepotent word dimension in the Stoop task. Interestingly, Sommers and Huff (2003) provided some evidence that these very different measures may indeed be related. They found that after controlling for age and overall processing speed in the Stroop task, the performance in the incongruent condition in Stroop actually predicted the likelihood of false recall in the DRM paradigm. We have considered these results consistent with both an attentional control framework for interpreting Stroop and false memories in the DRM paradigm (see Figure 18.2).

The Power of Stroop Errors in Prediction and Discrimination

As noted earlier, Spieler et al. (1996) showed that Stroop error rate increased in early stage AD compared to healthy older adults. At one level, this is not terribly surprising given that early stage AD individuals produce lower performance on a wide variety of tasks. The more important question is whether Stroop error rates provide particularly powerful discrimination between healthy aging and early stage AD. This was tested in a study by Hutchison, Balota, and Duchek (2010), who developed a Stroop switching task, which places considerable demands on the attentional control system. On each trial in this task, participants are cued to respond to either the
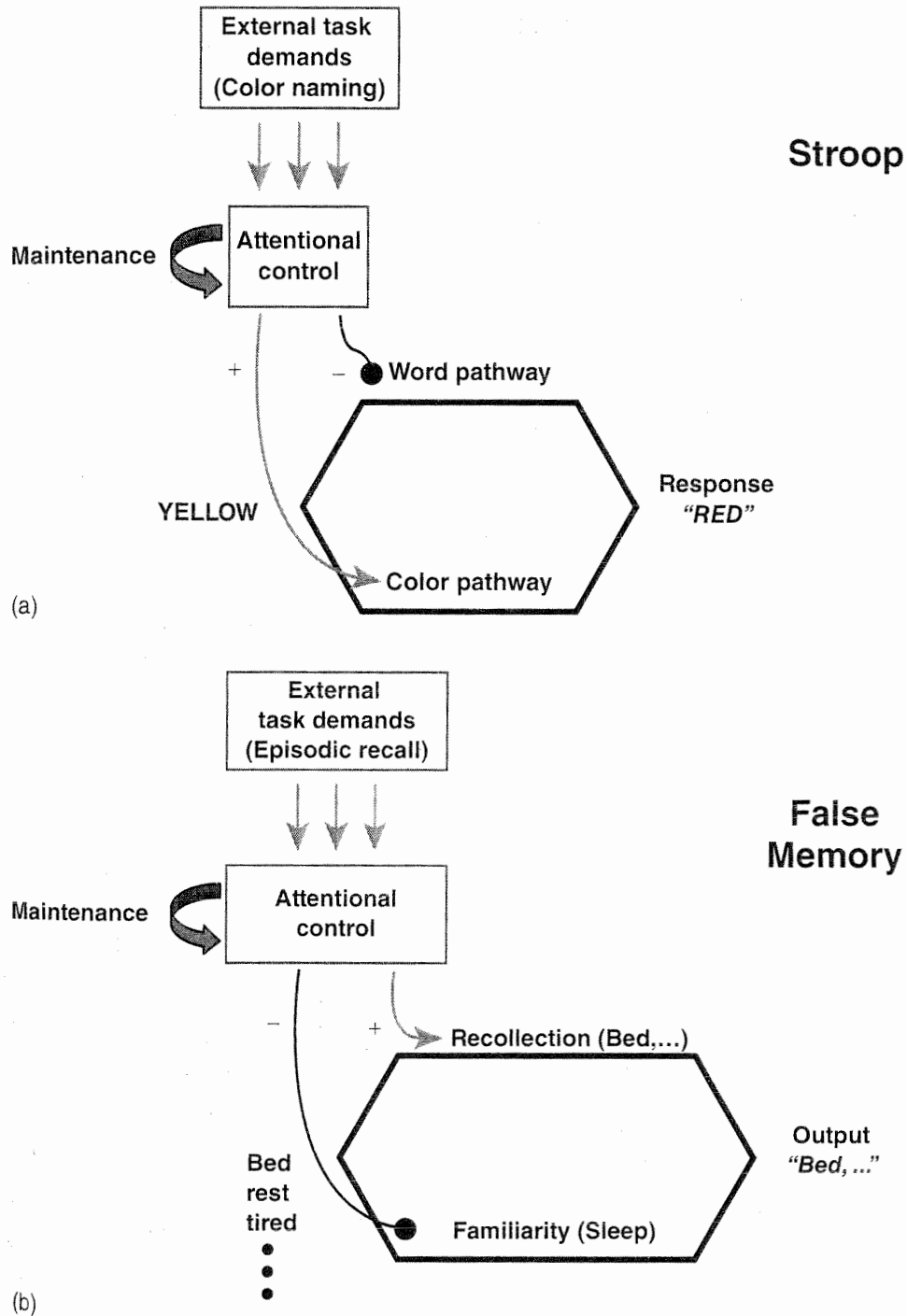
FIGURE 18.2 The attentional control framework applied to (a) the Stroop color-naming task and (b) false memory paradigm.

word or color dimension of the stimulus via a precue, and these cues switched every other trial in a Word, Word, Color, Color, Word, Word ... sequence. The important finding from this study was that the error rate in this task discriminated healthy control individuals from early stage AD individuals better than any of the 18 standard psychometric tasks that were available on these participants, which included

multiple measures of episodic memory, processing speed, and general fluid intelligence. This was demonstrated through the use of a logistic regression analysis, in which the error rate in the Stroop switching task produced a reliable increase in discrimination above and beyond each of the other psychometric tasks. The only task which produced a reliable increase in discrimination above and beyond the error rate in the Stroop switching task was the selective reminding task (a measure of episodic memory, see Grober, Buschke, Crystal, Bang, & Dresner, 1988).

The next question addressed was whether there is any predictive power of Stroop error rates for later conversion to early stage AD, when individuals are still healthy non-demented older adults. Fortunately, because of the longitudinal nature of the work at the Charles F. and Joanne Knight Alzheimer's Disease Research Center at Washington University, we were able to investigate whether any of the healthy control individuals that were tested in 1993 and 1994 in the Spieler et al. (1996) original Stroop study, actually converted to AD in the subsequent 14 years (see Balota et al., 2010). Given the age-related increase in AD and the fact that many individuals when healthy controls have AD pathology already building up (see Morris et al., study noted above), we would expect some individuals to convert to early stage AD over this time period. Indeed, of the 47 individuals that were followed, 12 converted to early stage AD in the subsequent years. Interestingly, the error rate in the incongruent trials discriminated those non-demented healthy control individuals who later converted from those who did not later convert. In addition, those individuals who converted also produced rather exaggerated slow tails of the RT distribution (see further discussion below) in the incongruent condition, compared to those individuals who did not convert. Importantly, none of the episodic memory measures was able to discriminate between converters and non-converters, and the only psychometric measure that did reliably discriminate between the two groups was the WAIS block design task which has little, if any, episodic memory demands, at least as traditionally conceived.

RT Variability and RT Distributional Components

Heretofore, we have been primarily emphasizing the utility of Stroop error rates as a useful marker. However, one aspect of attentional control systems that is critical is the ability to maintain the appropriate task set across time, see the maintenance recycling function in Figure 18.2. Researchers often assume at least implicitly that if a participant "understands" the instructions of the task, as reflected by a relatively low error rate, then this indicates that the correct attentional set has been engaged, and is engaged at the same level across trials and at the same level across individuals within the task. However, it is also possible that the integrity of the control system may wax and wane across trials within a task and this may vary across individuals. Indeed, even our best undergraduate students will sometimes produce an error in a Stroop task, which may reflect a trial

in which the control system (i.e., read the color) is no longer sufficiently established to overcome the prepotent word response. In fact, De Jong, Berendsen, and Cools (1999) have shown that if one simply decreases the response to stimulus interval in a Stroop-type task, the Stroop effect is reduced, presumably because there is not sufficient time for the attentional set to decay between trials (also see Jackson & Balota, 2013).

If the attentional set does vary across time, one might expect this to produce increases in reaction time variability. There is now accumulating evidence indicating that variability above and beyond mean performance is a useful marker for discriminating healthy aging from early stage AD (e.g., Dixon et al., 2007; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Hultsch, Strauss, Hunter, & MacDonald, 2008). For example, in one study, Duchek et al. (2009) investigated three attentional selection tasks (Stroop, Simon, and task switching) in healthy young, older adults, and in individuals with early stage AD. There were clear effects of both aging and AD status for these attentional control tasks on the coefficient of variation (standard deviation divided by the mean RT to control for overall speed differences). Hence, variability does indeed increase above and beyond what one would expect based on changes in overall response latencies. Duchek et al. suggested that this increase in RT variability may reflect changes in the integrity of the attentional control system across trials as a function of both age and early stage AD status.

A breakdown in attentional control may not simply predict an overall change in scaling the RT distribution, i.e., an overall increase in the variability in the reaction time distribution, but rather predicts an increase in the frequencies of the RTs in the slow tail of the RT distribution. That is, if on a given trial, the attentional set degrades then recovery of that set may produce an extraordinary cost in response latency, throwing that RT out in the tail of the RT distribution. In order to test this possibility, we have been investigating the shape of reaction time distributions by fitting an ex-Gaussian function to a participant's empirically obtained RT distribution (see Balota & Yap, 2011). The ex-Gaussian approach assumes that RT distributions can be considered as convolutions of two distributions, a Gaussian distribution, reflected by the mean (Mu) and variance (Sigma) and an exponential distribution, reflected by the exponential (Tau) component (see Figure 18.3). One appealing aspect of the ex-Gaussian function is that the mean of the RT distribution is constrained to be the algebraic sum of Mu plus Tau. So, if a variable influences Mu, this would reflect a shift in the total distribution, whereas, a variable that influences Tau, would primarily influence the tail (related to skewing) of the RT distribution.

Tse, Balota, Yap, Duchek, and McCabe (2010) fit the ex-Gaussian function to the data from the three tasks in which Duchek et al. (2009) found age and AD differences in the coefficient of variation, described above. The results are displayed in Figure 18.4. As shown here, age influenced all three parameters, whereas AD status only influenced the tail of the RT distribution, as reflected by changes

in Tau. Hence, these results suggest that in these three tasks, AD is marked by an increase in the tail of the RT distribution. This is at least consistent with the hypothesis that breakdowns in the maintenance of attentional control systems produce increases in the tail of the RT distribution due to recovery of task set in AD. Importantly, Tse et al. were able to provide converging evidence regarding this hypothesis. Specifically, these same participants also received three measures of working memory, which has been intimately linked to attentional control (see Engle & Kane, 2004). Through the use of structural equation modeling, Tse et al. were able to show that there was a strong link between Tau and the latent variable based on the working memory measures (reading span, computation span and rotation span), whereas there was no link between Mu or Sigma with the same latent variable. This provides some converging evidence consistent with the notion that breakdowns in attentional control in these tasks produce increases in skewing of the RT distributions. Interestingly, the strong relationship between the Tau parameter and the working memory construct was also found in an earlier paper by Schmiedek, Oberauer, Wilhelm, Süß, and Wittmann (2007) who also
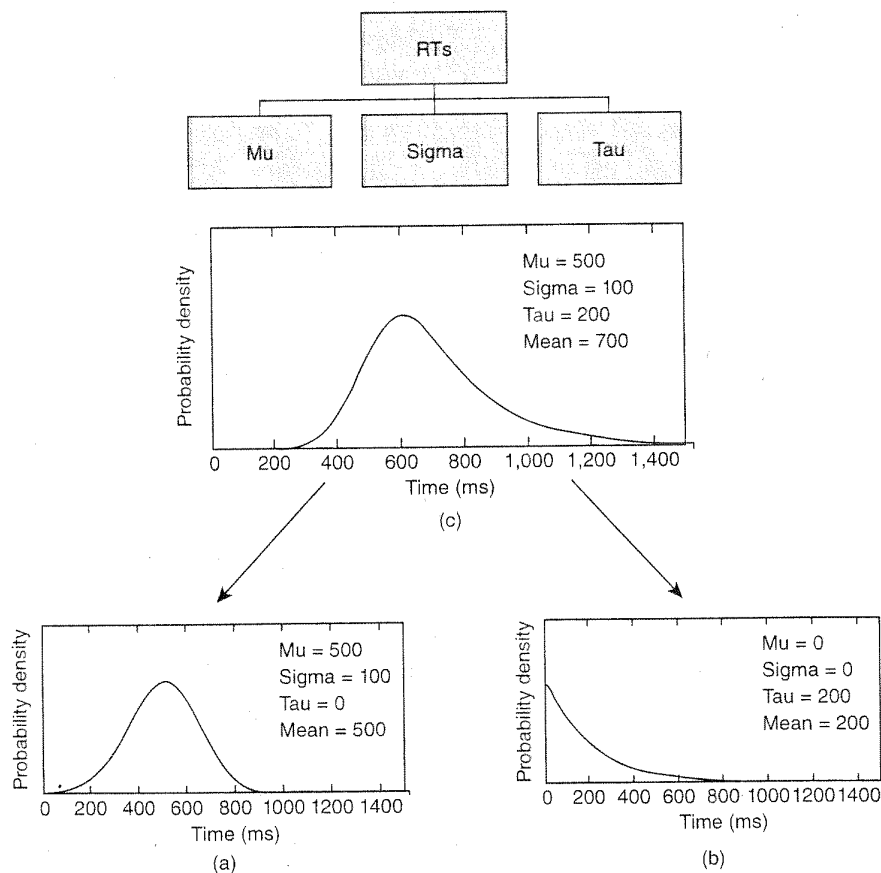

FIGURE 18.3 The relationship between the Gaussian (a) and exponential (b) functions and the ex-Gaussian function (c). The ex-Gaussian can be fit to empirically obtained RT distributions, to obtain estimates of Mu and Sigma (from the Gaussian) and Tau (from the exponential).

used structural equation modeling on the results from a wide variety of tasks to investigate the relationship amongst the ex-Gaussian parameters and working memory measures.

There are two additional points to note here about the utility of RT distributional measures. First, Jackson, Balota, Duchek and Head (2012) have shown through magnetic resonance imaging (MRI) volumetric measures of white-matter integrity that the RT distributional measure of Tau in these three tasks was most strongly related to white-matter volume. Interestingly, the cortical areas where the relationship was strongest were in areas, especially the precuneus, which have also been identified as important in the default mode network, described further below. Second, there is some intriguing evidence from the intelligence literature suggesting that slowest RTs are most strongly related to fluid intelligence. Specifically, if one ranks RTs from the fastest to the slowest within an individual and then correlates across individuals the different RTs with an individual's fluid intelligence measures, the correlation between fluid intelligence increases as the RTs increase, i.e., it is the slowest RTs that are most strongly related to fluid intelligence measures (see Coyle, 2003). This has been termed *the worst performance rule*.

As always, one needs to be somewhat cautious about inferences drawn from these studies. Specifically, it is clear that the demands of the tasks will modulate these relationships. For example, semantic priming appears to shift the entire RT distributions in high-functioning students, as opposed to producing an increase in skewing of the RT distributions (see Balota, Yap, Cortese, & Watson, 2008). Moreover, even within attentional selection tasks, there are different components of RT distributions that are differentially sensitive to the interference from conflicting dimensions. For example, although the incongruent trials in Stroop increase the tail of the RT distribution compared to the congruent trials, the incongruent trials in the Simon task increase the early portions of the RT distribution compared to the congruent trials, at least in younger adults (see Castel, Balota, Hutchison, Logan, & Yap, 2007; Pratte, Rouder, Morey, & Feng, 2010). Here we simply extend Jacoby's caution about process purity to ex-Gaussian estimates, and note that careful task analyses are necessary to understand the relationship between RT distributional components and attentional mechanisms. Ultimately, formal models that generate RT distributions will be critical (such as Ratcliff's, 1978, diffusion model) in taking the next step in understanding the relationship between characteristics of RT distributions and underlying mechanisms.

Biomarkers: The Next Step

Because AD is a progressive disease, there is considerable effort underway to identify early biomarkers that may presage the later development of the disease. There are multiple approaches in this area. First, researchers have been attempting to identify genetic markers for late-life Alzheimer's disease, and indeed have
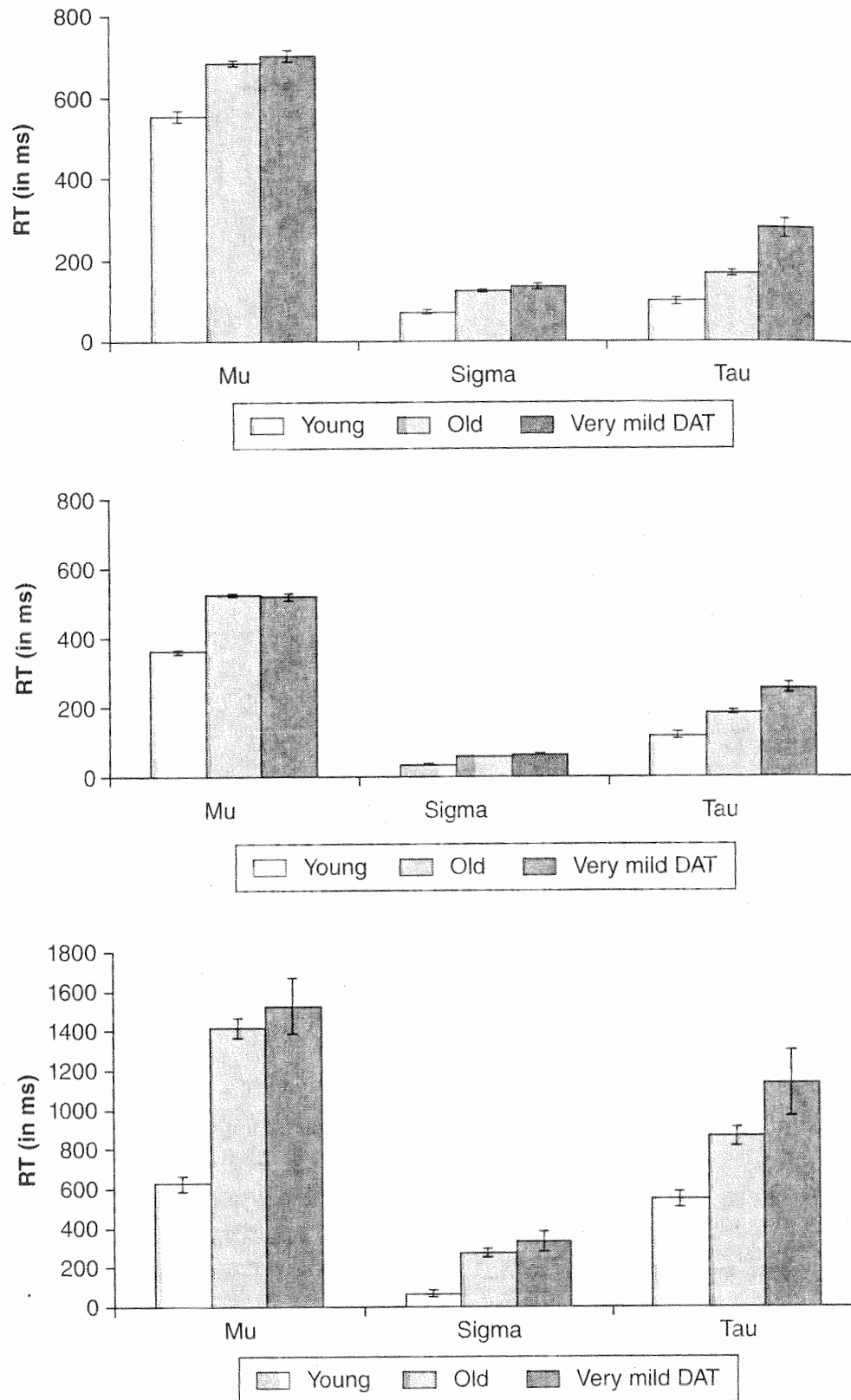
FIGURE 18.4 The ex-Gaussian parameters in (a) Stroop, (b) Simon, and (c) switching tasks as a function of group. Error bars indicate standard errors of means.

identified a relatively powerful marker, Apolipoprotein E (APOE) ε4 (e.g., Corder et al., 1993). If one has one ε4 allele, this increases the risk for developing AD 3–4 times and two ε4 alleles increases the risk by about 12 times. Second, as noted earlier, researchers have developed imaging techniques that now allow one to view amyloid building up in vivo in the brain. This is an important breakthrough because previously such neuromarkers were only available after autopsy. This is referred to as Pittsburgh Compound B (PIB) imaging (see Klunk et al., 2004). Interestingly, this measure has shown that some healthy older non-demented individuals have amyloid accumulating, and it is likely that these individuals are at increased risk for later developing AD, although how much risk needs to be confirmed by longitudinal studies which are currently underway. Finally, researchers have developed measures of the cerebral spinal fluid (CSF) that are sensitive to the amyloid and tau, two proteins that are correlated with the presence of plaques and tangles in the brain, respectively (e.g., Fagan, Roe, Xiong, Mintun, Morris, & Holtzman, 2007). Ultimately, the hope is that one will be able to identify biomarkers that provide a profile of an individual on an AD trajectory while they are still healthy. These individuals would likely benefit the most from therapeutic interventions, before the damage to neural structures takes place.

This recent interest in biomarkers nicely dovetails an important development in neuroimaging referred to as resting-state functional connectivity. Researchers have identified networks of activity as participants are being scanned, without being engaged in a specific task. By network here we are simply referring to activations in distinct areas of the brain that are correlated across time, such that when area A becomes activated area B also becomes activated. Multiple areas appear to cohere in their activation patterns, hence defining a network. One of the most powerful networks identified in this research is the network mentioned above, referred to as the default mode network, which is a network that is most active when participants are not engaged in a task (see Raichle et al., 2001). Once the participant engages in a task, this network is suppressed and an alternative network or networks come on line, which are most relevant to accomplishing the goals of a given task.

The coupling of work in the area of biomarker research and resting-state connectivity is very exciting. For example, one early study by Lustig et al. (2003) found that healthy older adults were less able to suppress the default mode network when a task is engaged compared to younger adults. In addition, individuals with early stage AD actually increased activity within the default mode network once the task began. Clearly, this network appears to be sensitive to both age and AD status. Recent studies have confirmed the sensitivity of the default mode network to AD biomarkers. For example, Sheline et al. (2010; also see Sperling et al., 2009) have shown disruptions in the default mode network in individuals with high amyloid burden as measured by PIB imaging. Moreover, Wang et al. (2013) found that CSF markers were associated with reduced default

mode network functional connectivity. Importantly, both of these studies are in healthy non-demented control individuals. These are indeed very important observations in understanding the influence of AD biomarkers on a critical neural network.

Of course, given the preceding discussion of cognitive changes in early stage AD, an obvious next question is whether there is any relationship amongst the neuropsychological measures that are available on these individuals, relevant biomarkers, and resting-state networks. Although the biological substrates correlated with the disease are critical to understand, how these markers relate to the cognitive breakdowns is ultimately the gold standard. It is important to note that at the onset, this may be a relatively weak relationship because the measures of cognition are taken in different sessions from the biomarkers and at a considerable interval (typically on average one year).

Duchek et al. (2013) have recently reported a study examining the relationship amongst biomarkers, resting-state connectivity, and cognitive measures. The target population in this study is a relatively large sample ($N = 189$) of healthy older adults who do not have any overt signs of dementia, but are being longitudinally followed on a wide set of measures. Four different resting-state networks were investigated. Here we will focus on the default mode network, which, as noted earlier, has been the target of a number of recent studies relating AD biomarkers to network integrity. The first set of analyses simply addressed whether any of the cognitive or neuropsychological tests were related to resting-state networks. Out of 15 measures investigated, there was only one task that produced any evidence of the targeted relationship and that was Stroop accuracy performance and the Tau component from the ex-Gaussian reaction time distributional analyses, described above. Importantly, these relationships were modulated by the presence of a CSF biomarker in an important way. These data are displayed in Figure 18.5. Here we break down the data into two groups of participants, those individuals who have low values of CSF $A\beta_{42}$ and those who have high values of CSF $A\beta_{42}$. Low CSF $A\beta_{42}$ is now a well-established biomarker for the development of AD, since this suggests that the brain is accumulating $A\beta_{42}$ (related to the development of plaques in the brain), thereby lowering it in the CSF. As shown in the right side of Figure 18.5, there is no relationship between Stroop error rates or Stroop RT distributional Tau estimates and default model network connectivity for those individuals who have normal CSF $A\beta_{42}$ levels. However, if one considers the participants who have low values of CSF $A\beta_{42}$ on the left side of Figure 18.5, one finds the predicted relationship. Specifically, as error rates and the tail of the RT distribution (Stroop Tau) increase, default mode network connectivity decreases. This is precisely the pattern one would predict regarding the relationship amongst cognitive control measures, CSF biomarkers, and resting-state connectivity measures. Importantly, the available memory measures from a psychometric battery on these same individu-
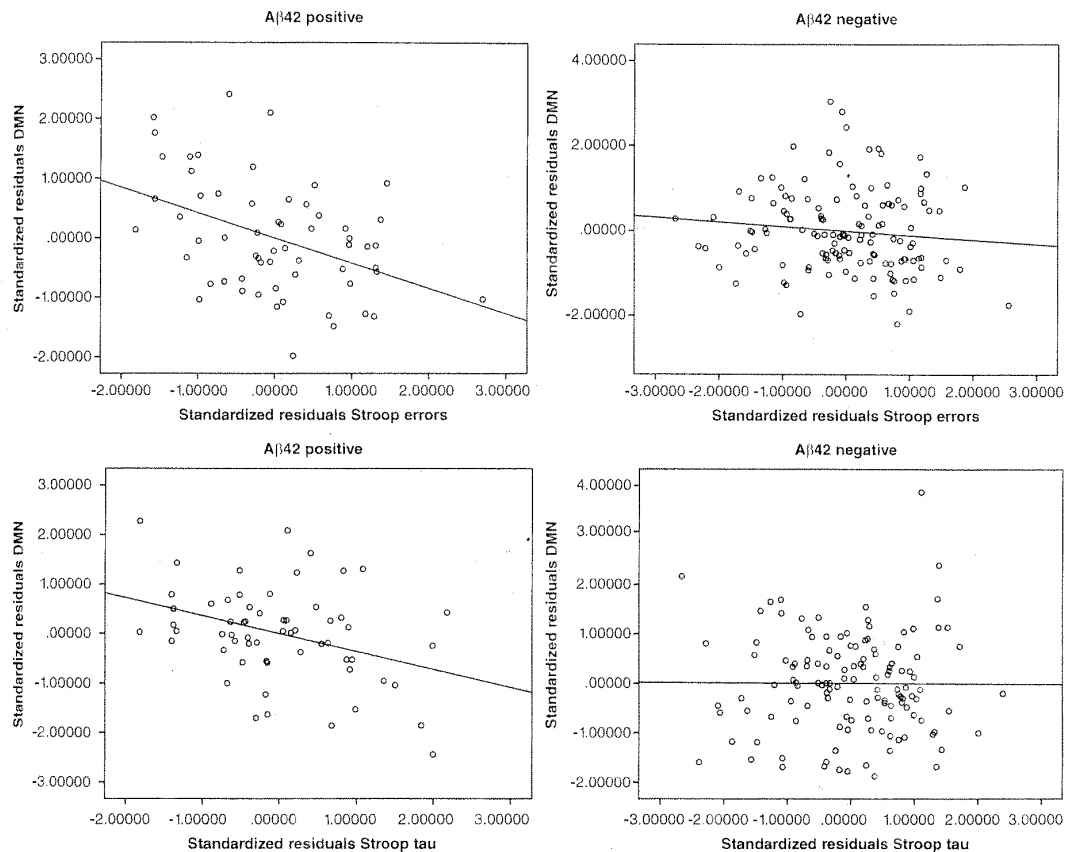
FIGURE 18.5 Scatterplots of standardized residuals for cerebrospinal (CSF) $A\beta_{42}$ positive (<500 ng/ml) and CSF $A\beta_{42}$ negative (>500 ng/ml) participants for Stroop errors and DMN (top row) and Stroop Tau and DMN (bottom row).

Conclusions

The goal of the present chapter was to provide an overview of recent research investigating changes in attentional control systems and their potential sensitivity to the accumulating biomarkers in AD research. We have surveyed a series of measures including attentional control, memory, brain volume, resting-state connectivity and biomarkers of AD. Clearly, this is a highly interdisciplinary endeavor. It is clear that Jacoby's emphasis on task analyses, the relationship between attention and memory, and the assumptions of process purity arm cognitive psychologists with tools to contribute to this important endeavor.

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