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Neurometabolism and cognitive functioning in healthy children : a proton magnetic resonance spectroscopy study

April Lightsey

April Brown Lightsey

Candidate

Psychology

Department

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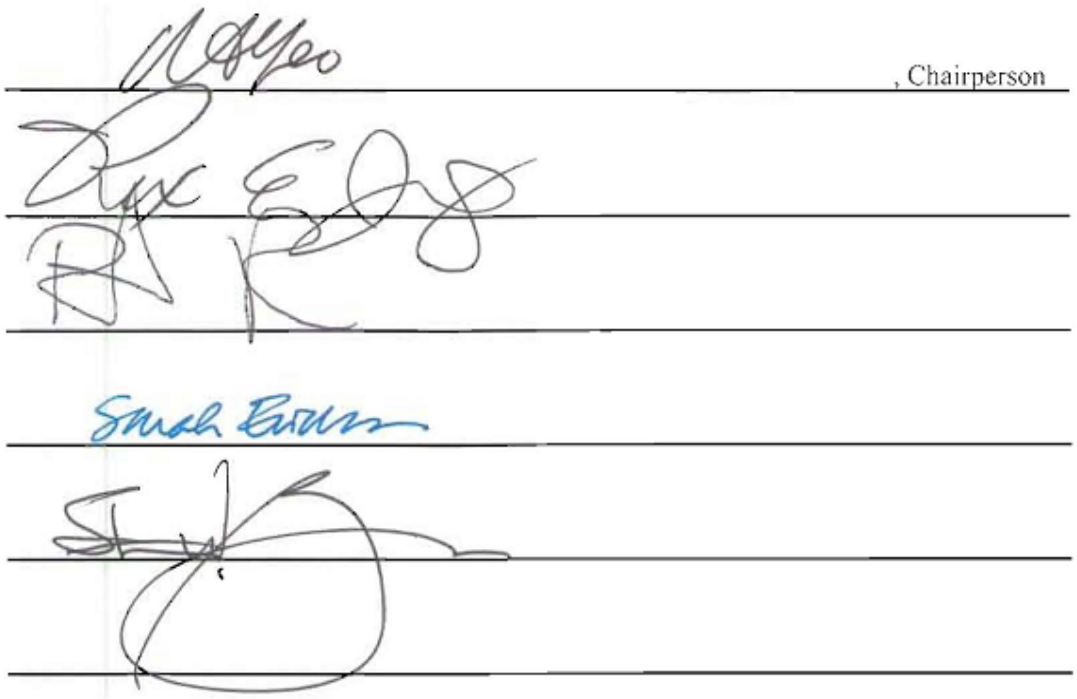

, Chairperson

NEUROMETABOLISM AND COGNITIVE FUNCTIONING IN HEALTHY CHILDREN: A PROTON MAGNETIC RESONANCE STUDY

BY

APRIL J. LIGHTSEY

B.A. Humanities, Biola University, 1991
M.S. Psychology, University of New Mexico, 2008

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
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ABSTRACT

This study investigated the role of sex, mean NAA/Cr and Cho/Cr, and variability in these metabolites in predicting memory and processing speed. This study utilized predictive models including sex, mean ratios of NAA/Cr and Cho/Cr, as well as the standard deviation of these ratios, within tissue type, among voxels in a supraventricular slice. In addition, models included interaction terms between each neurometabolic variable and sex. Tests of memory and processing speed were then regressed in a three-step hierarchical regression onto sex, main effects for neurometabolites, and interaction effects. The regression of memory was significant in the model including interaction terms, and showed higher mean NAA/Cr and lower standard deviation of NAA/Cr in gray matter related to better memory performance in boys, with the reverse pattern in

girls. Lower standard deviation of NAA/Cr in the white matter was related to faster processing speed for both sexes. A model including sex, Cho/Cr mean and standard deviation by tissue type, and sex by Cho/Cr interactions significantly predicted memory performance. No model using Cho/Cr predicted processing speed. Posthoc analyses suggest that tests of working memory showed stronger relationships to metabolites than tests of learning. Moreover, relationships may differ by sex depending on whether digit span or spatial span is the working memory variable of interest.

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Introduction

Healthy cognitive functioning is related a number of important psychological outcomes across intellectual, interpersonal, and vocational domains (Gottfredson, 1997). Understanding the neuroscience of healthy cognitive development could potentially create important pathways for improving human life in a variety of domains as well as giving us better insight into the diversity of human experiment. The purpose of this investigation is to examine the relationship between neurometabolism, memory, and processing speed in children. Memory function, including working memory and long-term memory, and processing speed are cognitive processes closely related to intellectual functioning (Chen & Li, 2007; Conway, Cowan, Bunting, Therriault, & Minkoff, 2002; Kaufman, DeYoung, Gray, Brown, & Mackintosh, 2009; Waiter, *et al*., 2009).

Although these cognitive domains have been the subject of extensive research and theorizing, their relation to neurometabolism in the healthy brain is largely unexamined in children. Furthermore, the use of proton magnetic resonance spectroscopy (^{1}H-MRS) to study cognitive functioning may have left some important variables on the table. In particular, sex is often underconsidered in ^{1}H-MRS studies. Furthermore, all research to date has focused entirely on mean values of neurometabolites, when variability of neurometabolism is also capable of being assessed and may make an important contribution to functioning.

Working Memory

The Construct of Working Memory

Memory functions can be meaningfully divided into short-term/working memory and long-term memory. Working memory is the capacity to hold information in attention

for the purposes of examination and manipulation. The most widely accepted model of working memory can be traced to an influential paper by Baddeley and Hitch (Baddeley, Thomson, & Buchanan, 1975), which describes a tripartite system involving a visuospatial sketchpad for the storage of visuospatial information, a phonological loop for the manipulation of verbalizable information, and a central executive for attentional control and manipulation of information.

This model has proved itself useful and robust over more than thirty years of research (Baddeley, 2003). The dissociation of visual and verbal storage has been supported by research suggesting that the storage of verbal information does not interfere with the storage of visuospatial information, and vice versa (Baddeley, 2003). Furthermore, the visuospatial sketchpad and phonological loop have distinctive properties, as will be discussed more below.

The phonological loop involves the rehearsal of verbalizable information for the purpose of short-term retention or processing. In adults, even words are pictorially presented are retained in a verbal system and rehearsed through subvocal articulation. One well-known result is the phonological similarity effect, which refers to confusion in short-term memory based on the similarity in sound between stimuli rather than similarities in form or meaning, an effect disappears given interference with articulation of the information to be retained (Coltheart, 1993; Murray, 1968).

Additional evidence for the phonological loop is the word-length effect, first described in a classic paper by Baddeley and colleagues in 1975. In it, Baddeley demonstrates that, rather than simply holding a certain number of “chunks” of information, working memory is limited by the duration of the presentation of the

material to be retained. Memory span is decreased when the words have more syllables, or when the duration of the word is longer, controlling for number of syllables and phonemes. Baddeley found that span can be effectively predicted by the number of words that the research subject could articulate in 2 seconds. When words were presented visually but rehearsal was prevented by requiring the subject to repeat an unrelated sound, the word length effect disappears, suggesting that a rehearsal mechanism sharing resources with articulation of sounds is the usual means of maintaining material in working memory, a means that can be supplanted with a visual memory system when the phonological loop is not available (Baddeley, *et al*., 1975).

The word-length effect is well established, although its theoretical significance continues to be explored. More recent formulations (Cowan, Wood, Nugent, & Treisman, 1997) suggest that while shorter duration is related to greater span, greater complexity of information also increases retention in working memory. This position deemphasizes simple decay in working memory and emphasizes interference effects. Arguing from studies that find the meaning and phonological structure of a word to be as important to verbal span as duration, Neath accepts the word-length effect as a limited phenomenon, but rejects that it necessitates a rehearsal-based view of working memory, suggesting that working memory, like long-term memory, is cue-driven (Nairne, 2002).

The analog of the phonological loop is the visuospatial sketchpad. In recent formulations, the visuospatial sketchpad has been fractionated into separate visual and spatial short-term memory stores, in keeping with the ventral and dorsal streams of visual processing (McAfoose & Baune, 2009). Several lines of evidence support this division. Numerous studies have found double dissociations between visual and spatial short-term

memory stores in terms of selective interference, in which certain stimuli will interfere with memory in one store but not the other (Darling, Della Sala, & Logie, 2007; Klauer & Zhao, 2004). Tasks that compete for the central executive seem to interfere more with processing of spatial/sequential working memory than visual/simultaneous working memory (Rudkin, Pearson, & Logie, 2007). In addition, the development of the visual memory store appears to follow a different course than the development of spatial memory (Logie & Pearson, 1997).

Consistent with this distinction, it has been suggested that the visuospatial sketchpad can be divided into a visual buffer for perceptual input, an inner scribe for updating information about color and form, and a visual cache that represents translates dynamic information (Logie & Pearson, 1997). To date, structural models of the visuospatial sketchpad are based on analogies with the phonological loop, and the validity of this analogy is controversial (Baddeley, 2003; Hitch, 2002). For example, there is no finding comparable to the word-length effect (Hitch, 2002). Complexity of visual stimuli is related to working memory span such that more complex information is more difficult to retain than less complex information in both the visual (Luria, Sessa, Gotler, Jolicœur, & Dell'Acqua, 2010) and spatial (Kemps, 1999) domains. However there is not a simple, linear relationship between complexity and visual or spatial span. For example, memory for faces is sometimes better than memory for line orientation as both types of stimuli become increasingly complex (Jiang, Shim, & Makovski, 2008).

The central executive, though critical for the functioning of working memory, is the least well understood component (Baddeley, 2003; Hitch, 2002). The executive was originally conceived of a little more than a limited capacity workplace (Hitch, 2002).

With theoretical development, attention regulation has emerged as an important component of the central executive (Kane, Bleckley, Conway, & Engle, 2001). Baddeley has proposed a model with four functions: 1) focus, 2) dividing and switching attention, 3) connecting with long-term memory, and 4) an episodic buffer that "binds together information to form integrated episodes" (Baddeley, 2003). The episodic buffer is the newest element of Baddeley's central executive, and has the least empirical support (Towse, Hitch, Horton, & Kail, 2007). There has been some suggestion that simple span and complex span are theoretically distinct due to differences in executive demand, measuring short-term memory and working memory, respectively rather than a single construct. However, although complex span correlates somewhat better with measures of higher order cognition (Daneman & Carpenter, 1980), the underlying processes seem to be the same, creating some debate regarding the degree to which the distinction is meaningful (Unsworth & Engle, 2007).

Working Memory in Children

The above model of working memory is derived from work with adults. However, confirmatory factor analysis of a working memory battery with a sample of 700 children between the ages of 6 and 15 indicate that the tripartite structure proposed by Baddeley and Hitch is a good fit for this age group as well (Gathercole, Pickering, Ambridge, & Wearing, 2004). Differences do occur in the course of development, however. Among primary school children ages 6-10, age is strongly correlated to working memory tasks. This appears to be mediated by improvements in both processing speed and working memory storage capacity, which do not show a relationship in children when age is controlled for (Bayliss, Jarrold, Baddeley, & Gunn, 2005). Speech

rate has been shown to be related to working memory span in both children and young adults (Hulme, Thomson, Muir, & Lawrence, 1984), and the increase in working memory can be accounted for in part by increases in the rate of speech, theoretically due to the role of subvocal articulation in the phonological loop.

The robust finding of a relationship between working memory and rate of articulation does not occur in preschool children, suggesting that children of that age do not engage in subvocal rehearsal (Gathercole, Adams, & Hitch, 1994). In a related finding, young children appear to rely on the visuospatial sketchpad for short-term memory of nameable pictures, making the shift to the primary reliance on phonological memory by age 11 (Hitch, Towse, & Hutton, 2001). The working memory of children is also influenced by the development of attention regulation across childhood, including the ability to ignore distractions (Bunge & Wright, 2007) and the ability to switch attention between the storage and processing components of many working memory tasks (Barrouillet, Gavens, Vergauwe, Gaillard, & Camos, 2009).

The cause of the increase in working memory span is a matter of theoretical controversy, and several sophisticated models of working memory development have addressed this issue. In an influential paper, Case, Kurland, and Goldberg (1982) proposed that the total processing space of the individual remains constant over development, but that this space is shared by storage space and operating space. Early in development, they propose, operating space takes up more of the total processing space. However, as operations become more automatic and processing speed is this increased, operating space is reduced and more information can be retained in the storage space. In support of this hypothesis, they demonstrated that processing speed is correlated to

working memory span and adult span is similar to that of children when task difficulty is increased.

In contrast, Towse and Hitch proposed a task-switching model suggests that children with faster processing speed have improved performance on memory span tests simply because they require less time to complete the operation portion of the working memory test, so that they don't have to remember the information as long and so that they can devote more time to rehearsal (Towse, Hitch, & Hutton, 1998). In a test of this hypothesis, Towse and Hitch kept the difficulty constant but varied the length of time that children had to remember information by varying the order of the items, sometimes frontloading the lists to be remembered with longer processing tasks, leaving less time afterward to remember the information and sometimes beginning with short items, leaving more time to remember the information. There was a significant effect for time in counting span, operation span, and reading span. This model looks at the "longevity" or "endurance" of working memory as more fundamentally descriptive than the number of items it can contain (Towse, Hitch, Hamilton, Peacock, & Hutton, 2005; Towse, *et al*., 2007). However, even the original theorists recognize that "task switching is unlikely to provide a complete explanation of working memory span" (Hitch, *et al*., 2001) and that "there is not a 1:1 relation between processing duration and memory performance" (Towse, *et al*., 2007).

In Barrouillet's time-based resource-sharing (TBRS) model, the factors influencing the development of increased memory span are somewhat different. This model suggests that the memory traces must continue to be refreshed by redirecting attention to them, although not necessarily through rehearsal (Barrouillet, Bernardin, &

Camos, 2004). As the cognitive load of the processing task increases, attention is less able to disengage from the processing task and refresh the contents of working memory, leading to memory decay. In the TBRS model, therefore, there are three main limitations of working memory: amount of available attention, rate of decay, efficiency of switching attention from processing to reactivating working memory contents (Barrouillet, *et al*., 2004; Barrouillet, *et al*., 2009). Working memory development could therefore result from changes in any of these variables.

In their study of children ages eight, ten, twelve and fourteen years old, (Barrouillet, *et al*., 2009) found that a faster pace resulted in lower spans for each age group. A faster pace would make it more difficult to switch between processing and reactivation, and thus this finding is consistent with the TBRS model. Moreover, the effect of faster pace increased with age, suggesting that older children take more advantage of pauses between retrievals, presumably because of faster activation of working memory contents. Finally, "the increase in span related to variations in cognitive load was proportionate to the span levels, as testified by analyses conducted on log-transformed scores." This finding suggests that the attention switching component of working memory, closely related conceptually to the central executive, is central in the development of working memory and in setting the limits of working memory span across development (Barrouillet, *et al*., 2009). Another important implication of this model is that, although the stores continue to be conceived separately, by limiting span according to ability in attention switching, the possibility of cross-modality effects is reintroduced, an implication which has been supported by a finding that spatial

processing can disrupt verbal maintenance (Barrouillet, Bernardin, Portrat, Vergauwe, & Camos, 2007).

Neuroanatomy of working memory

Working memory function is dependent on a diverse range of neuroanatomical regions (Baddeley, 2003). Regions activated by span tasks tend to overlap with perception and processing areas for the type of material to be retained (Conway, 2003). For example, visual material activates the dorsal and ventral streams of visual processing (Ventre-Dominey *et al*., 2005). However, when the material in working memory must be manipulated, activation extends to other areas, especially the anterior cingulate and dorsolateral prefrontal cortex (Conway *et al*, 2002). The ventrolateral prefrontal cortex is involved in monitoring information in working memory, and particularly in evaluating whether a particular item is part of the set that belongs in working memory (Badre & Wagner, 2007).

Changes in the relationship between working memory and brain function occur across development. The ventrolateral prefrontal cortex and the intraparietal sulcus have been implicated as crucial for visuospatial working memory in adults in fMRI studies, and these areas become more involved in visuospatial working memory tasks in children as they develop (Bunge & Wright, 2007). By contrast, subcortical areas such as the thalamus and caudate nucleus are relied on by children for working memory functioning, and become less activated in working memory tasks with age (Bunge & Wright, 2007). Edin and colleagues (2007) used computational models to investigate the effects of cellular developmental changes on working memory-related brain activity and performance, then compared their simulated models to fMRI measures of working

memory in children and adults. They examined each of the following changes as possible explanations for increases in working memory: stronger fronto-parietal synaptic connectivity between cells coding for similar stimuli, faster conduction, stronger connectivity within a region, or increased coding specificity. Only the stronger fronto-parietal synaptic connectivity between cells coding for similar stimuli created a model that corresponded to changes in brain activity associated with childhood development of working memory as measured by fMRI.

Long-Term Memory

Neuroanatomy of Long-Term Memory

If information which has passed through working memory is to be recalled later, it must be encoded into long-term memory, a process that relies heavily on the medial temporal lobe (MTL). Indeed, all the structures of the MTL are involved in memory encoding (Squire, Stark, & Clark, 2004). Historically, the hippocampus has been implicated as a crucial structure in memory encoding, particularly after a series of classic investigations of H.M. and other patients who developed profound anterograde amnesia subsequent to excision of large parts of the MTL, including bilateral recision of the anterior hippocampus (Milner, Corkin, & Teuber, 1968; Scoville & Milner, 1957). More recent lesion studies continue to demonstrate that patients with hippocampal damage show intact working memory, but impairment in the formation of new long-term memories (Buffalo, Reber, & Squire, 1998). The contribution of the hippocampus to memory has been the subject of extensive theorizing, but appears to be involved in the temporal-spatial organization of experience into declarative memory (Bird & Burgess, 2008).

However, despite the critical role of the hippocampus in the formation of explicit memories, other MTL structures are also integrally involved (Squire, *et al*., 2004). Cortical regions neighboring the hippocampus—including the parahippocampal cortex, entorhinal cortex, and perirhinal cortex—have intricate interconnections with the hippocampus and interactions between the hippocampus and neighboring cortical regions are related to memory encoding in psychophysiological studies (Fell *et al*., 2001). In one study of patients with amnestic syndromes (Buffalo, *et al*., 1998), although lesions localized to the hippocampal formation or diencephalon did show impairment in memory encoding, impairment was much greater when the entorhinal cortex was also involved. The entorhinal cortex has been implicated in memory consolidation for a period of twenty years, using the famous faces test as a probe (Haist, Gore, & Mao, 2001). In this study, the hippocampus appeared to have minimal involvement in consolidation for these stimuli.

In a 2005 review, Buckley argues that in human studies attributing amnesia to hippocampal damage, there has also been damage to surrounding tissue, and this extrahippocampal damage is necessary to produce amnesia. Lesions to the perirhinal and entorhinal cortex, and particularly the perirhinal cortex, prevent memory consolidation in macaques. On the other hand, when the parahippocampal cortex is preserved, memory function is also essentially preserved, even in the presence of discrete lesions to the hippocampus and amygdala (Buckley, 2005).

The insular cortex also plays a role in memory. Animal studies demonstrate the role of the insular cortex in learning aversions (Miranda & Bermúdez-Rattoni, 2007). In humans, the insular cortex has been reported to be active in encoding but not object recall

(Hofer *et al*., 2007). The insular cortex has also been implicated in logical memory (Manes, Springer, Jorge, & Robinson, 1999). Patients with Post-Traumatic Stress Disorder (PTSD) have structural and functional differences in the insula which are related to verbal memory (Chen, Li, Xu, & Liu, 2009).

The frontal lobes have been found to be active during memory encoding (Grady, Bernstein, Beig, & Siegenthaler, 2002; Stebbins *et al*., 2002). Such encoding may be lateralized according to the verbalizablity of information to be encoded, with verbal material activating left MTL and prefrontal cortex, abstract patterns activating right MTL and prefrontal cortex, and faces showing a bilateral pattern (Golby *et al*., 2001). Further, case studies of encoding deficits after frontal lobe injury have been reported (Ward, 2003). Whether frontal lesions interfere with memory encoding in patients seems to be related to the precise location of the lesion, with posterior frontal lesions more likely to disrupt encoding than anterior lesions (Stuss & Alexander, 2005).

Damage to the diencephalon has been associated with the memory loss characteristic of Korsakoff's syndrome (Caulo *et al*., 2005; Mitchell & Dalrymple-Alford, 2006; Vann & Aggleton, 2004). Anterior and medial dorsal nuclei show the most consistent involvement in memory (Taber, Wen, Khan, & Hurley, 2004). Deficits in both recognition and familiarity were found in a 40-year-old man with bilateral anterior and medial thalamic lesions, although recognition was more impaired. Similarly, he showed impairment in both verbal and nonverbal memory, but greater impairment in verbal memory (Kishiyama *et al*., 2005).

Additional roles for the thalamus in memory have been suggested. For example, it has been proposed that the thalamus may be involved in memory for unique entities,

across episodic and semantic memory (Miller, Caine, & Watson, 2003). Other researchers suggest the thalamus may be involved in memory for temporal order. A task involving remembering the temporal order of objects, which has been found to be related to hippocampal processing, was found to be impaired with thalamic lesions in rats (Wolff, Gibb, & Dalrymple-Alford, 2006). Although the thalamus often associated with anterograde amnesia, the location of the lesion may determine whether new or old memories are most affected. In one series of experiments, rats with anterior thalamic lesions showed impairment in acquisition of new memories in the Morris Water Maze. Conversely, rats with lesions in the lateral thalamic nuclei (including the intralaminar nuclei) showed deficits related to the age of the memory, not showing impairment on recent memories, but rather showing impairment on retrieval of older memories (Lopez *et al*., 2009). Others have also found that anterior thalamic nuclei are specifically involved in acquisition of new spatial memories, although this group found lateral thalamic nuclei to be involved in spatial working memory as opposed to long term memory (Mitchell & Dalrymple-Alford, 2006).

Also in the diencephalon, the mamillary bodies have inputs from the hippocampus and outputs to the thalamus, suggesting possible involvement in memory circuitry and functioning. The long-established role of the mamillary bodies in Korsakoff's syndrome further supports this involvement, but the precise nature of their role in memory is just beginning to be understood due to the myriad difficulties in studying structures so small, with even smaller internal nuclei (Vann & Aggleton, 2004).

Although the medial temporal lobes may play a role in the short-term storage of memory, they are not considered to be the site of long-term memory storage (Murray &

Bussey, 2001; Squire, *et al*., 2004). Arguments for this conclusion are many, but include the relative preservation of older memories when an MTL lesion prevents the formation of new memories. For example, in their early case report of patient H.M., Scoville and Milner (1957) relate "this patient appears to have a complete loss of memory for events subsequent to bilateral medial temporal-lobe resection 19 months before, together with a partial retrograde amnesia for the three years leading up to his operation; but early memories are seemingly normal." The time-limited retrograde amnesia described here, typical of patients with MTL lesions, provides a partial rationale for the MTL as a temporary storage site.

Conceptually, memories are composites of some particular combination of percepts and actions. As in working memory, the contents of long-term memories are generally understood to be stored in the same regions involved in the perception or action generation of related information to be recalled. In other words, visual memory tends to be stored in the visual cortex (López-Aranda *et al*., 2009; Slotnick & Schacter, 2006), auditory memory in the auditory cortex (Winkler *et al*., 2002), emotional memory in the limbic cortex (Kwon & Choi, 2009), etc.

Many areas involved in memory encoding also participate in retrieval (Hofer, *et al*., 2007). The same hippocampal-parahippocampal network involved in memory encoding and consolidation also plays a critical role in retrieval (van Strien, Cappaert, & Witter, 2009). Functional MRI has shown that a memory network including the left hippocampus, left lingual gyrus, and right caudate nucleus plays a role in memory retrieval, whether the memory is autobiographical, episodic, or semantic (Burianova, McIntosh, & Grady, 2010).

The frontal lobes also play a role in memory retrieval in memory retrieval, particularly in strategic search and in inhibiting competing memories (Incisa della Rocchetta & Milner, 1993). In rats, frontal regions create impairments in retrieving previously learned information (Winocur & Moscovitch, 1999). In humans, patients with left posterior lateral and posterior inferior medial frontal lesions show deficits in free recall in a list learning task, with patients in the left posterior lateral group also showing an increased number of false positives in recognition memory (Stuss & Alexander, 2005). Active involvement of left prefrontal cortex during encoding of verbal material is associated with improved subsequent recall in children, similar to findings in adults (Chiu, Schmithorst, Brown, Holland, & Dunn, 2006).

In an elegant series of experiments, Moscovitch (1994) demonstrated that sequential finger tapping during encoding and retrieval interfered with number of words recalled on the California Verbal Learning Test, but not with rate of learning. Sequential finger tapping also interfered with letter fluency, but not category fluency. Both number of words recalled and letter fluency are associated with effortful, deliberate searching and, more generally, with the frontal lobes. By contrast, rate of learning and category fluency are more associated with temporal lobe functioning. Moscovitch interpreted these results to support two processes in memory retrieval, a relatively automatic process of memory retrieval mediated by the MTL, and a conscious, effortful process of memory retrieval mediated by the frontal lobes. In this model, other activities to which conscious attention must be directed limits the available resources that can be directed toward effortful (i.e., frontal) but not automatic (i.e., temporal) retrieval.

In a recent review of ERP research regarding controlled memory retrieval, Mecklinger (Mecklinger, 2010) argues that retrieval of memories involves binding the various components of memory together in response to a memory cue. He suggests that processes related to the effectiveness of the cue in the memory search are mediated by the frontal lobe, while processes related to enhancing the availability of the target memory and suppressing other, competing memories—a mnemonic equivalent of selective attention—is mediated by the posterior parietal cortex.

White matter pathways have also been investigated in relationship to memory. In a diffusion tensor imaging (DTI) study of 52 adults (ages 25-80), better white matter integrity as measured by apparent diffusion coefficient (ADC) within the frontotemporal white matter pathways was correlated with reaction time in a nonverbal memory task, but not with accuracy (Sasson, Doniger, Pasternak, & Assaf, 2010). Age related declines in processing speed and working memory correlate with DTI variables in frontal white matter, whereas poorer episodic memory retrieval in central white matter regions (Kennedy & Raz, 2009). In children ages 9-15, mean diffusivity (MD) in the left uncinate fasciculus correlated with free and cued recall in an auditory-verbal list learning task (Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009). Age did not correlate with MD in the uncinate fasciculus in this study. The right uncinate fasciculus did not correlate with the list learning task, nor did nonverbal memory correlated with MD in left or right uncinate fasciculus.

An obvious conclusion of this brief review of the neuroanatomical substrates of both working memory and long-term memory is that virtually every area of the brain is involved memory, an understandable finding given that the ability to manipulate and

learn from information in the environment is arguably one of the primary functions of a nervous system in any animal and one of the primary contributors to increased complexity of the brain across species. In understanding the neuroanatomy of memory regionally, it is important not to obscure the fundamental reality that memory involves networks, in which disparate regions of the brain communicate and coordinate with one another at every step (Burianova, *et al*., 2010; Rajah, McIntosh, & Grady, 1999; Simons & Spiers, 2003; van Strien, *et al*., 2009; White & McDonald, 2002).

Developmental issues in long-term memory

Developmental differences have been found in the encoding and retrieval of memories in adults. In a study of facial recognition, after making a judgment of pleasantness or unpleasantness, younger adults who showed greater recognition of faces showed greater activation in hippocampus bilaterally, orbitofrontal cortex, and the left temporal pole (Grady, *et al*., 2002). By contrast, older adults with greater recognition of faces showed greater activation in bilateral posterior temporal and occipital regions and the right prefrontal cortex. Other imaging studies have suggested that age-related declines in memories are associated with changes in the frontal lobe functioning as opposed to changes in the functioning of the MTL (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003; Stebbins, *et al*., 2002) .

Given these developmental differences in adults, it is reasonable to inquire whether similar differences exist in children and adolescents. There are clear behavioral differences between the memory abilities of children and those of adults. For example, researchers investigated differences in memory for pictures in which young adult and child participants (ages 7-8 years) were first shown common objects drawn in either red

or green ink (Cycowicz, 2001). Subsequently, they were shown another set of drawings in black ink, some of which were otherwise identical to the original drawings. Participants were asked to indicate whether a drawing was a member of the original set, and –if so—whether it was drawn in red or green ink. Young adults performed significantly better than children on both object recognition and recollection of the color of the ink. However, the advantage of the young adult participants relative the child participants was significantly greater on the recollection of the ink color than the recognition of the object, a result interpreted by the authors to reflect the greater involvement of the frontal lobes in the integration of contextual information into memory and the greater immaturity of frontal lobes relative to temporal structures in children.

Strategies involved in memory encoding and retrieval become more varied and effective with development (Schwenck, Bjorklund, & Schneider, 2009). Generally, strategic metamemory improves with development (DeMarie, Miller, Ferron, & Cunningham, 2004; Justice, 1985). Rehearsal improves with age (Frank & Rabinovitch, 1974; Gathercole, *et al*., 1994; Yamada & Yamaguchi, 1983). Categorization increases with age (Hota, 1983). Children's memory performance improves immediately with increases instruction in encoding strategies (Chiu, *et al*., 2006; Schlagmüller & Schneider, 2002), changes which may be reflected in greater frontal lobe engagement (Chiu, *et al*., 2006). Improvement in strategy appears to interact with development of basic memory capacity (as measured by simple memory span tests) in mediating improvements in long-term memory (DeMarie, *et al*., 2004).

Another behavioral difference in memory between children and adults is the tendency of children to rely more on verbatim memory than adults, for whom gist

memory predominates. The difference between gist and verbatim memory and the implications of the shift to greater gist memory is discussed by Brainerd and Reyna (2004) in a review of research related to Fuzzy Trace Theory. The transition from verbatim to gist memory is adaptive in several ways. Briefly, gist memory, which relates to the meanings of events, is more efficient than verbatim memory, which reconstructs the sensory experience of the event. This greater efficiency is demonstrable both during encoding and retrieval. Moreover, verbatim memories decay more quickly and are more susceptible to interference. Memory for both verbatim and gist memory improves during the school-age years. However, children have particular difficulty using meaning to organize information for recall, only developing this skill in adolescence. This difficulty is related in part to less developed cognitive skills, but also to less life experience, yielding fewer organizational schemas and fewer meanings attached to individual concepts by which they might be related to other concepts.

Despite the phenomenon of "childhood amnesia," that is, rarity of memory in adulthood for events occurring before the ages of 3 or 4, the preponderance of evidence suggests that children are able to encode a number of details into episodic memory beginning at the age of approximately 2.5 years (Fivush, 2002). However, they have difficulty organizing these memories into coherent narratives for recollection, a skill which develops gradually over childhood, heavily influenced by the modeling of structuring memory narratives by parents (Fivush, 2002).

Given the behavioral changes in memory that occur during childhood as well as physical brain development, it is not surprising that there are also changes in neural substrates of memory during the school-aged years. Central nervous system

development is characterized by a number of important changes, including early synaptic proliferation followed by pruning through adolescence, myelination begins in the most ventral & posterior regions and finishes with myelination of the frontal lobes well into the third decade of life, and changes in cortical thickness (Toga, Thompson, & Sowell, 2006). During childhood and adolescence, there are linear increases in white matter and nonlinear increases in gray matter in all lobes across childhood and adolescence (Giedd *et al*., 1999). Fractional anisotropy in frontal, parietal, and temporal hemispheric white matter increases during childhood and adolescence (Mabbott, *et al*., 2009). Furthermore, measures of white matter integrity, including those that change with development, are related to measures of verbal and figural memory (Mabbott, *et al*., 2009). Activation of MTL structures during memory tasks stays relatively constant after the age of 8, but prefrontal cortex activation increases across childhood and adolescence, and these increases correlate with improved memory performance (Ofen *et al*., 2007).

Processing Speed

In addition to memory, this study investigates processing speed in children. Although reaction time and other simple measures of processing speed exist, speed as investigated in this study refers to the speed of completion of relatively complex executive and motor tasks. Processing speed for such tasks has previously found to be related to brain health. For example, in a study of healthy older adults, ages 57-90, processing speed (derived from the Grooved Pegboard, Coding, Symbol Digit, and Category Fluency tests) was correlated with measures of cerebral integrity, such as gray matter volume and sulcal span (Kochunov *et al*., 2010).

Speed of performance on the Trail-Making Test, parts A and B, has long been associated with frontal lobe lesions (Demakis, 2004; Kubo *et al*., 2009; Shibuya-Tayoshi *et al*., 2007). However, recent fMRI studies of the TMT-A and TMT-B demonstrate involvement of widespread brain regions, including frontal, cingulate, and temporal gray and white matter (Zakzanis, Mraz, & Graham, 2005).

Verbal fluency measures also contribute to the measure of processing speed included in this study. Lesion studies demonstrate the importance of the frontal and temporal lobes for both phonemic and semantic fluency as well as the greater sensitivity of phonemic fluency to frontal lesions and of semantic fluency to temporal lesions. (Henry & Crawford, 2004; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998). Left-sided lesions are associated with greater impairment than right-sided lesions (Alvarez & Emory, 2006). Children also show a similar patterns of frontal activation during verbal fluency tasks, although they activate larger regions than adults (Gaillard *et al*., 2000). Although verbal fluency is strongly associated with the prefrontal cortex, many brain structures are involved in fluency tasks, including the temporal lobes (Birn *et al*., 2010; Halari *et al*., 2006), parietal lobes (Gauthier, Duyme, Zanca, & Capron, 2009; Vitali *et al*., 2005), premotor cortex (Basho, Palmer, Rubio, Wulfeck, & Müller, 2007; Vitali, *et al*., 2005), visual cortex (Vitali, *et al*., 2005), anterior cingulate (Basho, *et al*., 2007; Gauthier, *et al*., 2009; Halari, *et al*., 2006; Nosarti *et al*., 2009), thalamus (Basho, *et al*., 2007; Gauthier, *et al*., 2009; Halari, *et al*., 2006), basal ganglia (Gauthier, *et al*., 2009; Halari, *et al*., 2006; Nosarti, *et al*., 2009), and cerebellum (Basho, *et al*., 2007; Gauthier, *et al*., 2009; Paquier & Mariën, 2005; Silveri & Misciagna, 2000).

Motor speed is impaired in a number of conditions, including Attention Deficit/Hyperactivity Disorder (Cole, Mostofsky, Larson, Denckla, & Mahone, 2008), epilepsy (Aldenkamp *et al*., 2001), toxin exposure (Bruno, Wagner, & Orrison, 1993; Winneke, 1982), prematurity (Drobyshevsky *et al*., 2007) and low birth weight (Bathen *et al*., 2009; Skranes *et al*., 2007), HIV (Ragin, Storey, Cohen, Edelman, & Epstein, 2004), and traumatic brain injury (Kuhtz-Buschbeck *et al*., 2003; Wozniak *et al*., 2007). Neuroanatomical and imaging studies of pegboard tests are scarce. However, effective performance on the grooved pegboard is rationally related to the motor cortex, particularly the hand area (Crafton, Mark, & Cramer, 2003); the motor planning regions, including the frontal and medial cortex (Kuhtz-Buschbeck, *et al*., 2003); the visual cortex (Galletti, Fattori, Gamberini, & Kutz, 1999; Gamberini *et al*., 2009); and parietal and frontal areas involved in visuomotor integration (Iacoboni, 2006; Quintana & Fuster, 1993; Wolynski, Schott, Kanowski, & Hoffmann, 2009). Children improve on timed motor tasks, including pegboard tasks, until early adolescence, when their performance begins to approach adult levels (Largo *et al*., 2001).

Clearly, processing speed as measured by a diverse battery of timed tests also involves most brain regions and is therefore subject to influence by many of the same developmental processes discussed above regarding memory development. However, changes in myelination are perhaps particularly relevant in for processing speed, inasmuch as a primary function of myelin is the acceleration of neural impulses. Myelination begins in the second trimester of gestation and continues into life's third decade, following a general inferior to superior, posterior to anterior developmental pattern across the brain that is thought to be related to functional cognitive development

(Lehnroot & Giedd, 2006; Sowell, Thompson, & Toga, 2004). Myelination increases the effective connectivity of the brain and also impacts changes in regional brain size in ways that are still incompletely understood (Sowell *et al*., 2004). These changes are mostly complete by early childhood (Lehnroot & Giedd, 2006).

Sex differences

Although not without controversy, sex differences are a common finding in psychology (Hyde, 2007) and neuroscience (Cahill, 2006). Evidence for sex differences in memory are mixed. Large samples sometimes find a small male advantage in Corsi Block-Tapping, which is not detected in small or moderately sized samples (Pagulayan, Busch, Medina, Bartok, & Krikorian, 2006; Postma, Jager, Kessels, Koppeschaar, & van Honk, 2004). Males performed transformations in visuospatial working memory more quickly, but not more accurately, than females (Loring-Meier & Halpern, 1999). In the 1988 norming data for the children's version of the California Verbal Learning Test, girls outperformed boys at every age in more words recalled, more semantic clustering, and fewer intrusion errors (Kramer, Delis, Kaplan, O'Donnell, & Prifitera, 1997). In a study of the Auditory Verbal Learning (van den Burg & Kingma, 1999), among 225 Dutch school children, (112 boys / 113 girl; 6-12 years old), "a slightly better performance of girls than of boys was suggested; controlling for age, the estimated mean difference was 1.8 words ($.10 > p > .05$ in analyses for both test administrations)." Boys also made more errors than girls. The relationship between sex and object location memory tasks is complex, but after puberty women tend to have an advantage for object identity and object location (Voyer, Postma, Brake, & Imperato-McGinley, 2007).

Sex differences related to processing speed have also been found. Several studies have found a female advantage for verbal fluency (Burton, Henninger, & Hafetz, 2005; Gauthier, *et al*., 2009; Halari, *et al*., 2006; Hausmann, Schoofs, Rosenthal, & Jordan, 2009), although others have not (Hurks *et al*., 2006; Mathuranath *et al*., 2003; Regard, Strauss, & Knapp, 1982). The female advantage for verbal fluency appears to develop with age (Sincoff & Sternberg, 1988). Regarding motor speed, one study indicated that girls have an advantage on the pegboard (Waber *et al*., 2007) and another indicated a male advantage (Martins *et al*., 2005). Boys, but not girls, with ADHD show deficits in motor speed relative to their peers (Cole, *et al*., 2008). The Trail-Making Test is not associated with sex difference in most samples (Giovagnoli, 1996; Hays, 1995; Rosin & Levett, 1989; Tombaugh, 2004; Vlahou & Kosmidis, 2002), but a small male advantage has been reported in elderly Koreans (Seo *et al*., 2006).

^{1}H-MRS spectroscopy and major neurometabolites

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive technique that allows the investigation of neurometabolic conditions *in vivo.* ^{1}H-MRS exploits the magnetic properties of hydrogen nuclei to identify the presence and relative quantity of chemical groups. In the human brain, the strongest signals are given by N-acetylaspartate (NAA), choline (Cho), and creatine (Cre). Understanding the function of these compounds and the meaning changes in their concentration is fundamental to interpreting ^{1}H-MRS findings.

NAA is the most prominent peak on a typical ^{1}H-MRS spectrum. Because NAA is present almost exclusively in neurons (Bjartmar, Battistuta, Terada, Dupree, & Trapp, 2002; Uranjak, Williams, Gadian, & Noble, 1993), a common interpretation of declines

in NAA is neuronal loss. However, these declines at times underestimate neuronal death (Demougeot *et al*., 2001; Sager, Hansen, & Laursen, 2000). In other circumstances, changes in NAA may overestimate cell death, inasmuch as NAA levels can also be indicative of cellular dysfunction in intact neurons. Moreover, it has been demonstrated that mitochondrial dysfunction can also cause declines in NAA in the absence of cell death (Dautry *et al*., 2000; Demougeot, *et al*., 2001).

Baslow (2003) argues that the primary purpose of NAA is to serve as a molecular water pump for neurons. Large quantities of water produced by glucose metabolism must be moved out of neurons against a gradient, and Baslow suggests that this is done by the mechanism of cotransport, coupling this movement of water to the energetically favorable movement of NAA along its high intracellular-extracellular gradient. One important idea to note in this hypothesis is the close relation between the rate of NAA turnover and the amount of glucose being metabolized at any moment, although the relation between glucose demands and steady-state NAA concentrations is less clear. In addition, because NAA is manufactured only in neurons and catabolized only in oligodendrocytes, it may play a role in signaling between these cells (Baslow, 2000).

Another function of NAA is as a brain store for aspartate and acetate groups. Because aspartate in the NAA cycle is largely sequestered to that cycle and NAA-derived acetate groups are diluted within a large pool of acetate groups available from other sources, Baslow argues that this function is largely inconsequential (Baslow, 2003). However, others have argued that decreases in NAA in brain injury may result from increased hydrolysis to provide a source of acetate for myelin repair and energy at the site

of axonal injury (Cecil *et al*., 1998). This hypothesis may be especially credible in circumstances in which demand for acetate is high and stores are low.

Another prominent neurometabolite is choline. The choline signal is present in all major neural cell types, although in differing concentrations (Uranjak, *et al*., 1993). The primary constituents of the choline peak are free choline, which comprises only a small fraction of the signal, and glycerophosphorylcholine and phosphorylcholine, which are metabolites of phospholipids components of cellular membranes (Govindaraju, Young, & Maudsley, 1999). All internal and external cellular membranes are composed of a combination of phospholipids and proteins, although the ratio of lipid to protein differs by cell and membrane type. In keeping with a general finding of higher choline in white than gray matter (Dechent, Pouwels, & Frahm, 1999; Saunders, Howe, van den Boogart, Griffiths, & Brown, 1999; Tan *et al*., 1998), myelin had the highest phospholipid to protein ratio in the brain, roughly 4:1 (Aidley, 1998; Lodish *et al*., 2000).

Phospholipids function primarily as the structural material of the many membranes of cell, separating chemical reactions from one another and acting as the matrix within which proteins are embedded. However, choline compounds are not visible to spectroscopy while imbedded in cell membranes, but only when they have been unbound from these membranes into the surrounding fluid. These compounds also play two other roles of potential interest to psychology: they can serve as a precursor pool for acetylcholine synthesis, and their metabolites can amplify or suppress internal signaling through second messenger systems (Zeisel & Blusztajn, 1994).

The meaning of changes in the choline signal is not well understood. One possibility is that choline signals increase during membrane turnover, when free choline

is made available either as a product of membrane breakdown or as it is provided for the purpose of forming new membranes. In addition, changes in acetylcholine demand may exert an effect on available free choline.

A third major neurometabolite is creatine. Creatine is also present in all neural cells, although in vitro work suggests higher concentrations in oligodendrocytes (Uranjak, *et al*., 1993). The creatine signal (Cr) is composed of both creatine (Cr) and phosphocreatine (PCr). The Cr/PCr system participates in cellular bioenergetics in at least four ways. First, it is serves as a temporal energy buffer for the cell (Brdiczka & Wallimann, 1994; Saks, Ventura-Clapier, & Aliev, 1996; Wallimann & Hemmer, 1994). The hydrolysis of PCr to create Cr and inorganic phosphate (P_i) releases energy that can be appropriated for cellular work. Although this energy, like that of ATP, is ultimately derived from the oxidation of sugar, PCr reserves in a cell can provide energy and prevent the depletion of ATP during periods of high demand. Second, Cr/PCr can improve the thermodynamic conditions of ATP/ADP reactions by accepting or transferring phosphate groups and maintaining favorable reaction gradients both in the mitochondria, the site of ATP synthesis, and in the cytoplasmic sites of ATP utilization (Saks, *et al*., 1996; Wallimann & Hemmer, 1994). Third, Cr/PCr affects cellular metabolism by the release of P_i into the cytoplasm, which influences rates of glycogenolysis and glycolysis (Wallimann & Hemmer, 1994). Finally, PCr may serve as an energy carrier, transporting high energy phosphate groups from sites of synthesis to the specific subcellular compartments in which they are required (Saks, *et al*., 1996; Wallimann & Hemmer, 1994). In neurons, the importance of Cr/PCr would be expected to increase when distances between ATP source and ATPase increase, as has been shown

in other cell types (Ames, 2000). However, the role of this shuttle in CNS cells is as yet undetermined. The role of the Cr/PCr system described here is that it is intimately coupled with ATP/ADP to promote more efficient energy production, consumption, and localization.

Because ^{1}H-MRS sees both Cr and PCr as a single peak, the creatine signal can not strictly be interpreted as either an index of current energy use or available energy reserves. However, changes in the creatine signal are suggestive of changes in energy regulation in a voxel. Functionally, creatine changes may also be related naturally to the apparent neuroprotective effect of creatine, mediated presumably through its energetic functions (Andreassen *et al*., 2001; Brustovetsky, Brustovetsky, & Dubinsky, 2001), inasmuch as cells in distress may naturally increase creatine levels to combat cell damage in the same way that creatine supplementation combats this damage. Changes in total creatine level of a cell can be effected through changes in Cr uptake, trapping, and loss via creatine, with regulation of cellular creatine content most likely regulated through changes in Cr uptake (Snow & Murphy, 2001). However, there is some evidence that CNS tissue is not dependent on Cr transported from the blood, but may be able to synthesize Cr *de novo* from available materials (Snow & Murphy, 2001).

Naturally, most information about neurometabolite levels in humans is derived from adult populations. Information about changes in neurometabolite concentrations during childhood is sparse and conflicting. Kadota, Horinouchi, & Kuroda (2001) reported an increase in the NAA/Cho ratio in the white matter of children, particularly in posterior regions, while gray matter showed a decrease in the NAA/Cho ratio during the same period. By contrast, in both parietal white matter and occipital gray matter, Kreis,

Ernst, & Ross (1993), found dramatic increases in NAA/Cr and [NAA] in children of gestational age less than 100 weeks (≅ 1 year postnatal age), more gradual increases from 100 weeks to 300 weeks (≅ 5 years postnatal age) and nearly constant values into adolescence. [Cr] stayed nearly constant throughout this period, with a small increase near the time of birth. [Cho] decreased in a monoexponential curve, from concentrations of approximately 2.5 mmol at birth to an asymptote of roughly 1.3 mmol, reached at approximately 300 weeks gestational age. Similar findings were reported by van der Knapp *et al*. (1990) in looking at a paraventricular voxel containing mostly white matter. This group found NAA/Cre and NAA/Cho both showing rapid increases in the first three years of life, nearly constant values between three and twelve years of age, then gradual increases between twelve to sixteen years of age.

Neurometabolites and cognitive function

^{1}H-MRS abnormalities have been associated with a variety of neuropsychological conditions (Ross & Sachdev, 2004). The most common finding is decreased NAA in relevant brain regions. Reduced NAA or NAA ratios have been found in Alzheimer's disease (Kwo-On-Yuen *et al*., 1994; Moats, Ernst, Shonk, & Ross, 1994; Schuff *et al*., 1997; Schuff *et al*., 2002; Stoppe, Bruhn, Pouwels, Hänicke, & Frahm, 2000), autism spectrum disorder and developmental disability (Friedman *et al*., 2003), multiple sclerosis (Foong *et al*., 1999), schizophrenia (Bustillo *et al*., 2002; Deiken, Zhou, Corwin, Vinogradov, & Weiner, 1997; Fukuzako, 2000; Shirayama *et al*., 2010), temporal lobe epilepsy (Connelly, Jackson, Duncan, King, & Gadian, 1994; Mantoan *et al*., 2009), and traumatic brain injury (Garnett *et al*., 2000; Ross *et al*., 1998). These findings are

consistent with the hypothesis that NAA levels are an index of neural density, neural health, or both.

Although less common, changes in choline have also been associated with neurological and psychological disease. Regional increases in choline occur in patients with temporal lobe epilepsy (Connelly, *et al*., 1994; Pauli *et al*., 2000), HIV (Chang *et al*., 2002), and schizophrenia (Bustillo, *et al*., 2002). Conversely, decreases in choline have been found in developmental dyslexia (Rae, Lee, *et al*., 1998) and autism spectrum disorder (Friedman, *et al*., 2003). Mood disorders also have been associated with changes in choline concentrations (Ende, Braus, Walter, Weber-Fahr, & Henn, 2000; Kato, Inubushi, & Kato, 1998), although this finding is not universal (Gruber *et al*., 2003).

Of the three peaks most visible to ^{1}H-MRS, creatine shows the fewest correlations with neural pathology. Creatine has been reported to increase in traumatic brain injury (Ross, *et al*., 1998), schizophrenia (Deiken, *et al*., 1997), and temporal lobe epilepsy (Connelly, *et al*., 1994). In addition, several studies show regional increases in creatine with normal aging (Brooks *et al*., 2001; Leary *et al*., 2000; Pfefferbaum, *et al*. 1999.; Saunders, *et al*., 1999). Creatine shows a trend toward elevation in the frontal lobe in patients with HIV, and, along with choline, is strongly correlated with CD4 counts (Chang, *et al*., 2002). Conversely, creatine has been reported to decrease in the frontal lobe of patients with depression (Gruber, *et al*., 2003).

In addition to establishing neurometabolic abnormalities in a variety of pathological conditions, ^{1}H-MRS studies have explored relationships between neurometabolite concentrations and cognitive function within these conditions, including

Alzheimer disease (Chantal, Labelle, Bouchard, Braun, & Boulanger, 2002; Pfefferbaum, Adalsteinsson, Spielman, Sullivan, & Lim, 1999), attention deficit disorder (Yeo *et al*., 2003), chronic obstructive pulmonary disease (Shim *et al*., 2001), ecstasy use (Reneman, Majoie, Schmand, van den Brink, & den Heeten, 2001), HIV infection (Chang, *et al*., 2002), lead exposure (Trope, Lopez-Villegas, & Lenkinski, 1998), multiple sclerosis (Christodoulou *et al*., 2003; Foong, *et al*., 1999; Staffen *et al*., 2005), neuropsychiatric systemic lupus erythematosus (Brooks, Friedman, & Stidley, 1999), schizophrenia and schizophreniform disorder (Bertolino *et al*., 2000; Bertolino *et al*., 2003; Ohrmann *et al*., 2007), temporal lobe epilepsy (Ferrier *et al*., 2000; Gadian *et al*., 1996; Pauli, *et al*., 2000), Williams syndrome (Rae, Karmiloff-Smith, *et al*., 1998) and Wilson's disease (Tarnacka, Szeszkowski, Gołębiowski, & Członkowska, 2009). Although many fewer studies have explored correlations between neurometabolites and cognitive function in normal populations, such questions have not been entirely neglected (Jung, Brooks, *et al*., 1999; Jung, Yeo, *et al*., 1999).

Neurometabolite levels have been found to relate to memory in clinical conditions. Several investigators have found negative correlations between NAA concentration or ratios and memory functioning (Bertolino, *et al*., 2003; Chantal, *et al*., 2002; Christodoulou, *et al*., 2003; Gadian, *et al*., 1996; Pauli, *et al*., 2000; Reneman, *et al*., 2001). Lower NAA/Cr in the right hippocampus predicts memory impairment, even when the impairment is mild (Caserta, Ragin, Hermida, Wise, & Ahrens, 2008). In patients with right mesial temporal epilepsy, contralateral NAA/(Cr + Cho) is correlated with verbal memory (Mantoan, *et al*., 2009). In patients with left mesial temporal epilepsy, right-sided NAA/(Cr +Cho) did not correlate with verbal or nonverbal memory

scores (Mantoan, *et al*., 2009). In patients with multiple sclerosis, gray matter NAA/Cr in the frontal cingulate gyrus was positively correlated with scores on the Wechsler Memory Scales (Staffen, *et al*., 2005). Neurometabolites are also related to memory performance in patients with schizophrenia, with lower NAA associated with poorer verbal learning (Ohrmann, *et al*., 2007). There may be regional variation in the power of neurometabolite ratios to predict memory functions (Chantal, *et al*., 2002; Christodoulou, *et al*., 2003; Gadian, *et al*., 1996). It is unclear if correlations exist between neurometabolic variables and memory in healthy people. Working memory has been shown to correlate with right frontal NAA and Cr in healthy children (Yeo, Hill, Campbell, Vigil, & Brooks, 2000). Significant positive correlations have been reported between verbal memory and Cho/Cr (Elderkin-Thompson *et al*., 2004; Ferguson *et al*., 2002) and NAA/Cr (Ferguson, *et al*., 2002) in elderly samples, but others have not found significant correlations between neurometabolism and memory in healthy populations (Bertolino, *et al*., 2003; Charlton, McIntyre, Howe, Morris, & Markus, 2007; Valenzuela *et al*., 2000).

Executive function, also, has shown a relation to neurometabolite concentrations. In clinical populations, there is some indication that lower NAA/Cr may be associated with poorer executive function (Chang, *et al*., 2002; Christodoulou, *et al*., 2003; Foong, *et al*., 1999), with rising [Cr] perhaps driving this change (Yeo, *et al*., 2003). Again, findings are more ambiguous among the healthy population. While Valenzuela (2000) found a correlation between NAA/Cr in frontal white matter and executive and attentional tasks among the elderly, no relation was found between concentrations of

frontal NAA or Cr and the Continuous Performance task among normal children (Yeo, *et al*., 2003).

Processing speed is related to neurometabolic variables in patient populations. Decreased NAA and Cho were associated with decreased processing speed in a battery including Grooved Pegboard, Coding, Symbol Digit Modalities Test and Category Fluency (Kochunov, *et al*., 2010). There also appears to be a relation between neurometabolism and speed in healthy populations. NAA concentrations in the left occipitoparietal white matter have also been found to positively correlate with neuropsychological tests generally and most strongly with timed tests (Jung, Brooks, *et al*., 1999).

Most broadly, researchers may ask whether neurometabolites correlate with general indices of neuropsychological functioning. In right-handed children with temporal lobe epilepsy, researchers found that Verbal IQ correlated positively with left side NAA/(Cho+Cr) and Performance IQ with right side NAA/(Cho+Cr). Moreover, this relation held regardless of whether MRS or WISC scores fell within the normal range (Gadian, *et al*., 1996). In adults with multiple sclerosis, both NAA/Cr and NAA/Cho predicted an overall neuropsychological performance z-score, with a stronger relationship in the right hemisphere (Christodoulou, *et al*., 2003).

These studies are consistent with findings in healthy populations. A recent study found that NAA within right anterior gray matter inversely correlated with VIQ while NAA within the right posterior gray matter was positively correlated with PIQ (Jung *et al*., 2009). In older studies, NAA concentrations were found to positively correlate with PIQ and VIQ (Jung, Brooks, *et al*., 1999; Rae, Karmiloff-Smith, *et al*.,

1998), as well as Full Scale IQ (Jung, Brooks, *et al*., 1999). In addition, Cho concentrations have been found to be independently associated with PIQ the WAIS-3 subtests matrix reasoning, information, and letter-number sequencing. However, this pattern is not consistent with findings from two studies among the elderly. Ferguson *et al*. (2002) did not find a correlation between any metabolite concentrations and a general cognitive factor derived from a principal component analysis of the experimental test battery. Similarly, Valenzuela (2000) found no correlation between NAA/Cr and general verbal ability in the elderly.

Although most ^{1}H-MRS studies of human cognition examine adults, many spectroscopic studies of children have been undertaken (Cortese *et al*., 2006; de Cássia Ferreira Gonçalves *et al*., 2009; Gabis *et al*., 2008; Kulak, Sobaniec, Smigielska-Kuzia, Kubas, & Walecki, 2006; Kulak *et al*., 2009a; Rae, Lee, *et al*., 1998; Sajja & Narayana, 2008; Walz, Cecil, Wade, & Michaud, 2008; Yeo, *et al*., 2000; Yeo, *et al*., 2003). The interpretation of neurometabolic data is similar, regardless of developmental stage. In a study of 41 healthy children, (ages, 1 month-16 years) van der Knapp and colleagues (1990) found that NAA/Cr and NAA/Cho both show rapid increases in the first three years of life, plateau between three and twelve years old, then increase again after age twelve. Others have found Cho/Cr shows a decrease over the first sixteen years of life, with the greatest change in the first three years (van der Knapp, *et al*., 1990). Additionally, some researchers have found increases in NAA/Cr in the basal ganglia in children with spastic diplegia and also healthy control children ages 2-18 (Kulak *et al*., 2009b).

Another developmental change with potential importance for ^{1}H-MRS is myelination, which occurs into the mid-twenties. Myelination causes changes in the binding of water around the axon, which causes changes in the signals generated by magnetic resonance techniques, but the precise physiological implications of these signal changes are not yet well understood (Inder & Huppi, 2000).

Spectroscopic imaging (SI), or chemical shift imaging (CSI), yields metabolite concentrations or ratios from many voxels laid in a grid across the MR image. In theory, this allows for regional analyses not possible in single voxel MRS techniques. In practice, the signal-to-noise ratio is proportional to the size of the voxel, so that the smaller voxels sampled in SI are noisier and difficult to interpret. To decrease noise, several voxels sampled using SI techniques are typically averaged when CSI data are analyzed and reported, and some of the advantages of more data points are lost. Measuring variability in neurometabolism gives researchers another vantage point in understanding the relationship between neurometabolism and cognitive functioning. Lower variability could be advantageous, related to consistent control of cellular functioning across brain regions and fewer regional disruptions. However, an alternative model of parenchymal metabolism could be posited in which ideal neurometabolic ratios vary according to characteristics of brain structures. Children's brains possess more equipotentiality than adult brains, recovering better from focal injury and activating broader regions during cognitive tasks in functional neuroimaging studies. Decreases in variability could be related to maturity and the concomitant specialization that occurs. In this scenario, increased variability would be related to better performance.

Previously, we found that lower variance in NAA/Cr and Cho/Cr is related to better performance on timed tests in children with brain injury. However, both metabolic variance and slowed cognitive performance may be general measures of brain injury severity without a direct relationship between them. An examination of the relationship between metabolic variability and cognitive functioning in healthy children would clarify whether variability may itself be related to healthy functioning, independent of injury.

Hypotheses

This investigation's hypotheses fall into four categories: developmental changes in neurometabolites across the ages studied, sex differences in neurometabolic values, the relationship between neurometabolites and memory function, and the relationship between neurometabolites and processing speed. In terms of developmental changes, this investigation seeks examine whether mean NAA/Cr, mean Cho/Cr, the standard deviation of NAA/Cr, or the standard deviation of Cho/Cr will correlate with age. Past research suggests that they will not, but this area is underexplored.

Secondly, sex differences in the neurometabolic variables will be investigated. There are three reasons, discussed more fully in the introduction above, to examine this question: the frequency of sex differences in brain functioning (Cahill, 2006), sex differences in both memory functioning (Kramer, *et al*., 1997; Loring-Meier & Halpern, 1999) and speed of processing (Halari, *et al*., 2006; Martins, *et al*., 2005) that suggest the possibility of differences in the neurological substrates of cognitive functioning, and the possibility that sex differences, if they do exist, could weaken the predictive power of relationships between neurometabolism and cognitive functioning if not taken into account.

Additionally, the relationship between NAA/Cr, Cho/Cr and memory will be investigated. Research to date has been equivocal regarding a relationship between neurometabolism and memory in healthy subjects. As indices of CNS health, both NAA/Cr and Cho/Cr could show relationships with memory or working memory, which rely on distributed processing and white matter networks, many of which transverse the slice being examined. Although this study does not have the statistical power to test for

sex differences in the relationships between neurometabolism and memory, tests will be run both with all subjects and separately by sex in order to increase sensitivity should sex differences in the relationship exist.

Finally, the relationship between processing speed and neurometabolism will be investigated. Neuropsychological tests with a timed component have previously shown a relationship to neurometabolic variables (Jung, Brooks, *et al*., 1999). Given the same reasoning as above, these relationships will also be tested for the combined sample and by sex.

Methods

Participants

Participants (n=34) were will be children between the ages of 6 and 18 years old, with no history of brain trauma, neurological disease, schizophrenia, hypertensive encephalopathy, CNS infection, chronic metabolic disturbance, liver failure, uremia, kidney transplant, uncontrolled diabetes, or medication with neuroleptic drugs. To ensure safety in the magnetic resonance machine, participants who were or may have been pregnant or who had metal or electronic objects implanted in their bodies were excluded. Informed consent was obtained from the parents or guardians of the participating children. Children seven or older were given a separate assent form, which explained the procedures in terms comprehensible to children.

The participants ethnically reflected local demographics, which are approximately 50% Hispanic, 45% White, 2.5% Black, and 2.5%. Because they were matched to brain injured subjects due to their use as controls in another study, more participants were male than female, reflecting the epidemiology of traumatic brain injury.

Participants were recruited from relatives of children treated for traumatic brain injury at Carrie Tingley Hospital, with the assistance of Dr. John Phillips and Dr. Rick Campbell. Additionally, children were be recruited from the University of New Mexico subject pool, local private schools and nonprofit organizations, and recruitment flyers posted at the UNM Hospital as necessary.

Procedures

All children received a complete battery of neuropsychological tests. An magnetic resonance exam was also given, usually on the same day, but within two weeks if participants could not schedule both exams together.

Proton magnetic resonance spectroscopy

Acquistion of magnetic resonance images and spectroscopic data

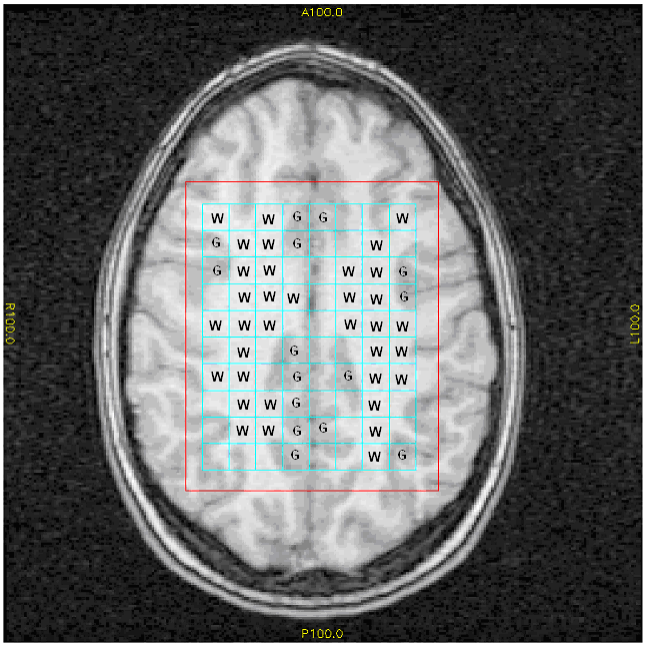


Figure 1. Prescribed slice from child in this study. The red box defines the region of interest (ROI) within which spectroscopic values were measured. To reduce noise from lipids in the skull, the most external voxels were excluded from analysis, leaving an effective ROI represented by the blue grid. Voxels that were approximately 70% or more one tissue type were identified and means and standard deviations were calculated separately for gray and white matter.

All studies were carried out using a 1.5 Tesla MR scanner at the MIND Imaging Center. The initial 13 studies were carried out on a GE scanner and final 21 studies were carried out on a Siemens scanner. The protocol was a T1-weighted volume axial series (fast-SPGR, TE=6.9ms, Tr=17.7ms, flip=25, 3mm slice) and a T2-weighted axial series (TE=30/100, Tr=2800ms, 3mm slices). A SI slice was selected above the lateral ventricles to extend from the frontal to the occipital and parietal lobes sampling both WM and GM. Water-suppressed PRESS localization with outer voxel suppression bands was used to excite parenchyma and avoid lipid artifact from the skull: 15mm slice, TE=62ms,

Tr=1500ms, 24*24 phase encoding matrix, 20cm FOV. Imaging of each participant took approximately one hour.

Analysis of spectroscopic data

Spectroscopic imaging data was transferred to a Sun Ultra SPARCStation (Sun Microsystems, Mountain View, CA) for analysis using LCModel (Provencher, 2001). Neurometabolites are reported as ratios: NAA/Cr and Cho/Cr. To minimize lipid artifact, data from both the GE and Siemens were smoothed using the proprietary software associated with each machine. The mean neurometabolite concentration and the standard deviation across voxels were calculated for each participant.

Neurometabolic values were excluded from analysis if outside specified parameters for LCModel processing (S. W. Provencher, 1993; S.W. Provencher, 2001) Voxels in the outer row or column of the region of interest were excluded from analysis because of poor fit variance in neurometabolic values, inasmuch as such variability was a variable of interest. In one case, an SI acquisition was rejected due to movement artifacts.

The image offset was determined and corrected for each image. Then the image was overlaid with a grid representing the voxels from which the spectroscopic values were prescribed. Each voxel was visually inspected. If the voxel appeared to be at least 70% one tissue type, it was designated either gray or white matter as appropriate. In ambiguous cases, tissue type was not assigned.

Neurometabolic variables

For each subject, mean values and standard deviations were calculated for gray and white matter. To increase power by decreasing the number of predictors and because

neurometabolic means were correlated across tissue types, gray and white matter means were standardized and averaged into a one variable for NAA/Cr mean and another for Cho/Cr mean. (The Pearson correlation coefficient for NAA/Cr in white and gray matter was .555, p=.001. The Pearson correlation coefficient for Cho/Cr in white and gray matter was .563, p=.012). Standard deviations were not averaged across tissue type.

Psychometric Tests

Children took the following tests as part of a neuropsychological test battery designed for a study of traumatic brain injury: the Hopkins Verbal Learning Test (HVLT); the Test of Learning and Memory (TOMAL); the Controlled Word Association test (COWAT); digit span forward and backward; spatial span forward and backward; the grooved pegboard test; the Trail-Making Test, forms A and B; and Contingency Naming.

Scores from each test was converted to a standard score based on previously published data when possible and appropriate. If published data did not include all ages in our sample, means and standard deviations necessary to calculate standard scores were estimated using regression equations created from available ages. Test data was used to create age-appropriate norms for the HVLT. Standardize test scores for all participants were averaged into two indices, Memory and Speed, and analyses were performed on each index.

Memory index

The memory index included scores from the HVLT Recall Immediate, TOMAL Story Immediate and TOMAL Faces Immediate, Digit Span Total, and Spatial Span Backward. The person taking the HVLT learns and recalls a list of twelve words, from three semantic categories. They are read and recall the list three times in the immediate

portion of the test. For the TOMAL stories test, the person taking the test listens to a story then must retell it to the test administrator. In the TOMAL facial recognition test, the person taking the test briefly examines faces, then must choose the faces he or she was shown from a matrix of photographs of faces. Digit span and spatial span are tests of verbal and spatial working memory, respectively. In the digit span forward test, the experimenter recites numbers and asks the subject to repeat them in the same order. In digit span backwards, the experimenter recites numbers, and the subject repeats them in reverse order. A similar procedure is followed in spatial span, but the subject is required to touch blocks in the same order that the experimenter has touched them, and then to touch them in reverse order. Digit and spatial span tests, particularly in the backwards condition, are sensitive to a wide variety of neurological impairments (Lezak, 1995).

Speed index

The speed index included all tests within the battery in which speed was the outcome of interest. This included the grooved pegboard test, the Trail-Making Test, Contingency Naming, and the COWAT Letter fluency and Category fluency. In Form A of the Trail-Making Test, the subject must connect circled numbers, which are randomly distributed across the page, in sequential order. In Form B of the Trail-Making Test, the subject must alternate between numbers and letters (1-A-2-B-3-C …). While both forms tap visuomotor skills and processing speed, form B also taps executive functioning, particularly shifting (Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003). The Contingency Naming test is a Stroop-like test that does not require reading. The examinee names either the color or shape of a stimulus in two naming conditions, a switching condition, and a complex switching condition. Total time can be used as an outcome score. T-

scores for the speed index, as well as the memory index, are indexed so that higher scores indicate better performance.

Statistical analysis

Statistical analyses were conducted in SPSS Version 16. Power analysis and effect sizes were calculated using GPower 3.0.10. The effect size measure f^2 was used, as recommended for regression equations (Cohen, 1992).

Results

Descriptive Statistics

Thirty-four healthy children and adolescents (22 male, 12 female) participated in the study and had both NAA/Cr and testing data available for analysis. The ages of these participants ranged from 6.9 to 19.0 years (mean age 13.7, standard deviation 3.66). A subset of this group (14 male, 7 female) also had Cho/Cr data available for analysis. Several memory tests were introduced while the study was in progress, and therefore the complete memory battery is not available for all subjects. One female participant with both NAA/Cr and Cho/Cr data did not complete testing due to test anxiety and therefore did not have any memory tests available for analysis.

Machine effects

A significant difference was found in the MRI machine used to test males and females for both the NAA/Cr analysis (38.5% male GE, 81% male Siemens, p=.011) and the Cho/Cr analysis (0% male GE, 78% male Siemens, p=.006). Two multivariate ANOVAs were performed to ascertain whether neurometabolite measures were influenced by the MRI machine used in imaging, first entering all the NAA/Cr variables as dependent variables, then entering all the Cho/Cr variables as dependent variables. Because machine and sex were correlated, both machine and sex was included as factors in the MANOVA. A significant effect was found for machine for measures of NAA/Cr ($F=15.464$, $p<.001$) and Cho/Cr ($F=4.150$, $p=.022$). See Table 1 for neurometabolite values by machine. To control for the machine effect, each of the neurometabolic variables was regressed onto machine, and the standardized residual was used as the

variable of interest. Correlations between corrected and uncorrected neurometabolite variables are found in Table 2.

Sex and Age

After controlling for machine effects in this way, a sex difference was found for the standard deviation of NAA/Cr in gray matter voxels (t=2.490, p=.019) and the mean of Cho/Cr in gray matter voxels (t=2.675, p=.016). Unstandardized, uncorrected neurometabolite measures are given by sex in Table 3. No sex difference was found for either memory (t= -.836, p=.410) or speed (t= -1.487, p=.147). Age did not correlate with any neurometabolite measure, although there was a trend toward an inverse correlation with mean Cho/Cr (r=-.400, p=.073). This trend disappeared after correction for machine effects (r=-.302, p=.182).

NAA/Cr and Cognitive Functioning

A hierarchical multiple regression of memory onto sex and NAA/Cr variables was carried out in three steps, entering first sex; then NAA/Cr mean, NAA/Cr standard deviation for gray matter voxels, and NAA/Cr standard deviation for white matter voxels; and finally, interactions between sex and each of the NAA/Cr variables (see Table 4). Results were not significant when only main effects were considered (R^2=.100, p=.551). However, when interactions were added to the model, the results were highly significant (R^2=.599, p=.001), with the interaction term between sex and mean NAA/Cr (p<.001) and between sex and the standard deviation of NAA/Cr in the gray matter (p=.009) driving the model.

Another way to examine this data is to perform separate regressions in the combined sample and by sex. The memory index was regressed onto mean NAA/Cr,

within subject NAA/Cr standard deviation for white matter voxels, and within subject NAA/Cr standard deviation for gray matter voxels as a block on the for all participants and then by sex (see Table 5). When this regression was performed on all research participants, the neurometabolite variables accounted for a small proportion of variance (R^2=.094, f^2=.103), and the regression did not attain significance (p=0.406). However, when this regression was performed within each sex, the proportion of variance increased and the regression attained significance for males (R^2=.385, p=0.030, f^2=.626) and females (R^2=.783, p=0.010, f^2=3.608). Combining information from the hierarchical regression and separate regressions by sex, it is evident that higher NAA/Cr mean and lower NAA/Cr standard deviation in gray matter is associated with better memory performance in boys, while lower NAA/Cr mean and higher NAA/Cr standard deviation in gray matter is associated with better memory performance in girls.

Similarly, a hierarchical multiple regression of speed on sex and (see Table 6). In this analysis, the strongest model included main effects only (R^2=.187, p=0.039). No benefit was found in adding interaction terms (R^2=.101, p=0.068). NAA/Cr standard deviation in the white matter showed the strongest relationship to processing speed, with lower variability related to faster processing speed.

Again, to clarify the relationship, the speed index was regressed on to mean NAA/Cr, within subject NAA/Cr standard deviation for white matter voxels, and within subject NAA/Cr standard deviation for gray matter voxels, entered as a block, on the for all participants and then by sex (see Table 7). In the entire sample, this regression attained significance (R^2=.282, p=0.018). The effect size was in the upper region of the small range (f^2=.392). The regression for males only had a similar effect size (f^2=.285),

that did not reach significance in the smaller sample (R^2=.222, p=0.200). The regression for females only had a large effect size (f^2=.1.409), that showed a trend toward significance, despite a sample of only twelve participants (R^2=.585, p=0.060). If NAA/Cr values uncorrected for machine are used as predictors, results are similar, except that significance in not attained for males in predicting memory (R^2=.278, p=0.111, f^2=.385) and significance is attained for females in predicting speed (R^2=.780, p=0.005, f^2=3.545).

Cho/Cr and Cognitive Functioning

As with NAA/Cr, a hierarchical multiple regression of memory onto sex and Cho/Cr variables was carried out in three steps, entering first sex; then Cho/Cr mean, Cho/Cr standard deviation for gray matter voxels, and Cho/Cr standard deviation for white matter voxels; and finally, interactions between sex and each of the Cho/Cr variables (see Table 8). As with the previous regression of memory on NAA/Cr, results were not significant when only main effects were considered (R^2=.623, p=.099). However, when interactions were added to the model, the results attained significance (R^2=.808, p=.037), with the interaction term between sex and mean Cho/Cr (p=.021) and between sex and the standard deviation of Cho/Cr in the white matter (p=.056) showing the strongest effects. When all variables are entered, lower Cho/Cr standard deviation in gray matter is associated with better memory for both sexes. Lower mean Cho/Cr is also associated with better memory for both sexes, but the slope is much steeper in females. Regarding the standard deviation of Cho/Cr in white matter, there is an inverse relation to memory performance in females and a small positive relation in males.

Among main effects that showed a significant relationship, the standard deviation of Cho/Cr in gray matter was related to speed whether interaction terms were in the model (R^2=-.466, p=.050) or not (R^2=-.621, p=.019). When interaction terms were excluded from the model, the standard deviation of Cho/Cr in white matter was related to speed (R^2=.529, p=.042). When interaction terms were included in the model, mean Cho/Cr in white matter was related to speed (R^2=.529, p=.042).

Post-hoc analysis of NAA/Cr and Memory

Given that networks underlying memory span differ somewhat from those underlying learning and long-term memory, the memory index was conceptually divided into a learning index (HVLT Recall Immediate, TOMAL Story Immediate and TOMAL Faces Immediate) and a span index (Digit Span Total and Spatial Span Backward) to aid in interpretation. Then, separately for each sex, the learning and span indices were regressed onto the NAA/Cr variables. NAA/Cr was not significantly related to learning for males or females, although there was a trend in females (R^2=.961, p=0.057, f^2=. 24.641) (see Table 6). Similarly, there were trends for significant relationships between NAA/Cr variables and span for both males (R^2=.339, p=0.065, f^2=. 512) and females (R^2=.591, p=0.084, f^2=1.44).

The span index was composed of Digit Span, which is typically an area of strength for females, and Spatial Span, which has been reported as an area of strength for males, although only in very large samples. Nevertheless, the possibility of sex differences in the span subtests motivated a further division in the span index to the individual scores, Digit Span Total and Spatial Span Backward. Digit Span Total was not significantly related to NAA/Cr mean and standard deviation in males (R^2=.258, p=.751,

f^2=.347), but the regression was significant in females (R^2=.705, p=.029, f^2=2.389). Conversely, the regression of NAA/Cr variables on Spatial Span Backward was significant in males (R^2=.517, p=.029, f^2=1.070), but not in females (R^2=.195, p=.705, f^2=.242).

Discussion

Interpretation of findings

Sex and age

After correcting for machine, this study found slightly lower Cho/Cr in girls than in boys. A similar result was found by Kulak (2009) in the healthy control children in their study, with girls showing higher NAA/Cr and lower Cho/Cr than boys. However, the majority of studies do not show sex differences in Cho between male and female subjects (Friedman *et al*., 2003, Kantarci *et al*. 2000, Saunders *et al*. 1999). In this sample, there was a higher standard deviation in NAA/Cr in the gray matter voxels of boys than in girls. Because standard deviation is a novel variable in spectroscopy studies, there is no relevant literature to which to compare this result.

Correlations between age and neurometabolite ratios generally yielded null results. The trend toward a relationship between age and Cho/Cr mean did not survive correction for machine effects. Although some small changes in neurometabolism have been reported with age, as discussed above, the greatest changes in neurometabolite ratios occur during the preschool years, with values in school-age children and adolescence similar to adult values (Kreis, *et al*., 1993).

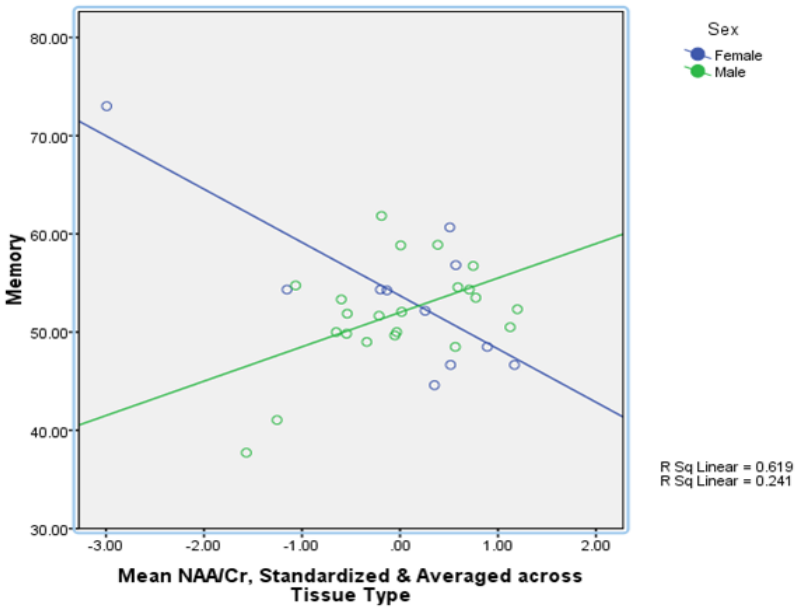
NAA/Cr and Memory

A hierarchical multiple regression of memory onto sex NAA/Cr variables revealed significant interactions of sex with neurometabolism in predicting memory. Moreover, separate regressions by sex revealed that the beta coefficients for NAA/Cr mean, which was the strongest contributor to the model, occurred in opposite directions for males and females, having a positive correlation with working memory in males and a

negative correlation in females. The effect size was somewhat larger in females. Males and females did not differ in working memory ability.

Figure 2

Regression of memory on mean NAA/Cr by sex



The relationship between NAA/Cr and memory is more complicated. In males, higher mean levels of NAA/Cr and lower standard deviations are related to better memory performance, both during spatial working memory and when memory is encoded into long-term memory for later retrieval. (However, this relationship does not hold for Digit Span, in which there is not a significant relationship between cognitive performance and the NAA/Cr model.) In females, this relationship holds for learning information and encoding it into memory. These results are consistent with a common finding of better cognitive performance with higher levels of NAA/Cr. In addition, although the use of within-subject standard deviation of NAA/Cr is relatively, the finding of lower variability being related to better performance is consistent with both our previous study of brain injured children and with the concept of NAA/Cr standard deviation being a good

measure of consistent regulatory control of neurometabolism and therefore of good developmental health.

However, in girls, there is not a significant relationship between NAA/Cr variables and spatial working memory, and better verbal working memory is predicted by *lower* mean NAA/Cr and *greater* variability, at least in the gray matter. These findings clearly cannot be interpreted the same way as the above.

The interaction between sex and working memory is an intriguing finding here. Consistent with earlier research (Martins, *et al*., 2005; Pagulayan, *et al*., 2006), this study did not find a significant sex difference in performance in working memory span (t=.134, p=.894), including when subdivided into performance on digit span total (t=-.178, p=.860) or spatial span backward (t=-.103, p=919). However, others have found sex differences in working memory when the tasks become more difficult (Cattaneo, Postma, & Vecchi, 2006; Duff & Hampson, 2001). This suggests the possibility of sex differences in working memory networks which only become evident when the system is taxed. Sex steroids are reported to have effects on working memory function in older adults (Janowsky, Chavez, & Orwoll, 2000) and it is possible that differences in sex steroids during development have an influence in working memory at earlier ages. The absence of functional differences does not rule out structural differences. In a helpful paper, DeVries (2004) argues that structural brain difference often exist to maintain similar behaviors in males and females, compensating for functional differences that would otherwise exist due to hormonal differences between the sexes. He gives examples of both differentiation and compensation of behavior as a result of brain-related sex differences. Direct genetic effects, independent of the sex steroids, may also account

for gender differences in brain structure and functioning (Arnold, 2003, 2004; Dewing, 2003).

Furthermore, previous research on brain structure and metabolism has found sex differences in their relationship to cognitive measures. For example, one study found a relationship has between white matter volume and both processing speed and verbal ability in as sample of ten boys but no relationship between brain tissue volumes and cognition in girls (Yurgelun-Todd, 2002). In contrast, a greater number of gray matter voxels were correlated with IQ in male adult subjects than female adult subjects in a study using voxel based morphometry, while the reverse was true for white matter voxels (Haier, Jung, Yeo, Head, & Alkire, 2005). Sex differences in correlations between neurometabolism and cognition are similarly inconsistent. Pleiderer and colleagues (Pfleiderer *et al*., 2004) found a positive correlation between NAA and VIQ in women, but not men in dorsolateral prefrontal cortex and left anterior cingulate. In sample of 17 male and 10 female healthy subjects, NAA in the left frontal and left occipito-parietal white matter strongly predicted IQ in female but not male subjects (Haier, *et al*., 2005). Jung *et al* (2009) found higher NAA correlated to higher PIQ in males and females, but lower NAA correlated to higher VIQ in males and females, trending toward a stronger relationship in males. Lower overall NAA/Cr combined with higher variability in NAA/Cr across voxels suggests a strategy of efficiency, in which networks are pruned and bioenergetics differ according to local demands. In such a scenario, if resources were properly allocated, overall NAA/Cr could be reduced without impairment of function.

NAA/Cr and Processing Speed

A hierarchical multiple regression of speed on NAA/Cr variables was not improved by interaction terms. An NAA/Cr model including only main effects of neurometabolic variables significantly predicted processing speed in the combined sample of males and females. A similar small effect size was found in males but did not reach significance. A large effect size in female participants showed a trend toward significance. In this model, standard deviation of NAA/Cr in the white matter had the strongest relationship with processing speed, with a smaller standard deviation predicting better performance. Male and female participants did not differ in cognitive measures of processing speed.

Tests of higher-level processing speed have been shown to be related to structures captured in the slice from which neurometabolites were measured, structures including the cingulate gyrus, superior frontal gyrus, middle frontal gyrus, and superior parietal lobule. In addition, a number of white matter tracts also transverse this slice, including callosal fibers, the superior region of the corona radiata, the superior longitudinal fasciculus, the superior region of the internal capsule, the superior thalamic radiation, as well as short-range association fibers. Because the tasks involved in the processing speed measure involve widely distributed networks, the health of the white matter tracts transversing this slice is likely to be an important contributor to processing speed.

It is worth noting that mean NAA/Cr was not related to processing speed, but that standard deviation of NAA/Cr, which has not been previously utilized as a variable of interest was related to speed of processing. That is, children with less variability in NAA/Cr within their gray and/or white matter tended to have faster processing speed in

complex tasks. Because measures of neurometabolic variability are essentially unexplored, the significance of this finding is necessarily speculative. However, the finding suggests that, within a given individual, the ratio of NAA/Cr should be relatively constant, and that disturbances in development that create uneven patterns of neural density or energetic signify disruptions of healthy functioning in the same way that excessive asymmetries can be suggestive of developmental disturbance. Alternatively, high variability in NAA/Cr, as reflected in larger standard deviations, could indicate weaknesses in the distributed networks underlying complex cognitive functions that need to be performed quickly.

Cho/Cr and Cognitive Functioning

Similar hierarchical multiple regression analyses were carried out entering sex, Cho/Cr mean, Cho/Cr standard deviation within white matter voxels, and standard deviation of Cho/Cr within gray matter voxels and interaction terms between sex and all three Cho/Cr variables. The regression of memory on these variables was significant only when all variables were included in the model; a model for main effects only was not significant. The regression of speed on these variables did not attain significance. The discussion of the importance of sex interactions in the regression of memory on NAA/Cr variables is equally relevant here.

Interpretation of the Standard Deviation Variable

Because standard deviation in neurometabolites has not been used as a variable of interest in previous research, interpretation of the variable is difficult. However, there have been other investigations that have indicated regional variation in neurometabolites. For example, greater NAA has been reported in the thalamus than the telencephalon

(Braun *et al.*, 2002). In rats, glutamate differs between the basal ganglia and cerebellum, and the direction of this difference is dependent upon whether water or creatine is used as a reference (Ronen *et al*. 2009). Finally, NAA has shown different relationships to cognitive performance depending on whether it is located in anterior or posterior voxels (Jung *et al*. 2009).

Simple models of mean NAA related unidirectionally to better cognitive functioning are increasingly likely to be found inadequate. Similarly, variability is likely to be complex in its relation to cognition. Some variability between tissue types and regions is likely to occur even in healthy brains. Nevertheless, limits in the degree and location of neurometabolic variance are logically also necessary to healthy neuropsychological functioning. Furthermore, this study suggests that these differences may differ according to sex. Developmental differences, although not found here, are almost entirely unexplored and may provide additional theoretical insights.

Limitations of the study

This study had several limitations. Perhaps most notably, a small number of subjects reduced the power available to explore relationships among the variables. A larger sample would allow a greater exploration of the data. Further, several relationships with large effect sizes failed to attain significance. A larger sample could clarify whether such relationships are due to random effects in a small sample or, rather, would attain significance. Another limitation of this study is the use of ratio data rather than water-standardized "absolute" concentrations for each metabolite. Use of absolute values would allow cleaner interpretation of the relationships between metabolites and

cognition. In addition, the method parceling gray and white matter used in this study was crude, introducing noise into the analysis that would be absent given a more finely grained parcellation procedure. The use of ratio data and visual inspection for parcellation was necessitated by the transition from the GE to the Siemens MRI machine, a transition which also introduced a machine effect not fully explained. This unexplained variance, which necessitated statistical correction, is another limitation of the study. The test battery was not originally constructed for the examination of memory and processing speed in healthy children. As a result, more complex measures of working memory and more simple measures of processing speed were not available for analysis.

Implications for further research

This study suggests that neurometabolic variability is a variable of interest in predicting cognitive outcomes, yet it has been previously unused in published research. Continued investigation of neurometabolic variability and its meaning may well be a fruitful addition to spectroscopic methods. Because this variable is essentially novel, many unanswered questions remain regarding its significance, including its developmental course and relationship to other measures of both neural health and cognitive functioning. When higher variability is associated with better cognitive functioning, ideal patterns of neurometabolites, particularly patterns co-registered with the underlying neuroanatomy, is worth seeking out. Such a pattern would support an efficiency explanation for the advantage of higher variability in neurometabolism.

Another implication of this study is the importance of considering sex. Interactions between sex and neurometabolism were crucial to the predictive power of spectroscopy in this study. Excluding sex would have resulted in more null results, and it

would not be possible to interpret the data coherently if sex were not included in the analysis. This suggests possible pitfalls in interpreting spectroscopic data while excluding sex as a variable of interest.

Speed and working memory are closely related constructs, as better processing speed contributes to larger working memory span and both constructs are related to intellectual functioning. However the results of the relationship between neurometabolites and these constructs were not unambiguously consistent. A more detailed analysis of the relationship between these variables as they are related to neurometabolism is warranted, as is an exploration of the relationship of these variables to intelligence. Spectroscopic studies of intelligence have found posterior regions to be of particular importance. Similar regional analysis may be of value in exploring the relationship between processing, working memory, and neurometabolites.

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Appendix

Table 1

Neurometabolite measures, by machine

	GE			Siemens		
Neurometabolites	n	M	SD	n	M	SD
Mean NAA/Cr, White matter	13	1.36	.165	21	1.62	.107
Mean NAA/Cr, Gray matter	13	1.32	.170	21	1.35	.100
SD of NAA/Cr, White matter	13	.248	.059	21	.194	.033
SD of NAA/Cr, Gray matter	13	.258	.058	21	.223	.056
Mean Cho/Cr, White matter	3	.350	.020	18	.324	.034
Mean Cho/Cr, Gray matter	3	.227	.027	18	.230	.033
SD of Cho/Cr, White matter	3	.087	.039	18	.045	.007
SD of Cho/Cr, Gray matter	3	.068	.034	18	.044	.011

Table 2

Correlations of neurometabolite measures, uncorrected and corrected for machine

Neurometabolites	r
Mean NAA/Cr, White matter	0.699
Mean NAA/Cr, Gray matter	0.995
SD of NAA/Cr, White matter	0.855
SD of NAA/Cr, Gray matter	0.952
Mean Cho /Cr, White matter	0.960
Mean Cho /Cr, Gray matter	0.999
SD of Cho /Cr, White matter	0.675
SD of Cho /Cr, Gray matter	0.859

Table 3

Neurometabolite measures, by sex

	Males			Females		
Neurometabolites	n	M	SD	n	M	SD
Mean NAA/Cr, White matter	22	1.56	.144	12	1.46	.239
Mean NAA/Cr, Gray matter	22	1.34	.102	12	1.34	.174
SD of NAA/Cr, White matter	22	.219	.049	12	.208	.057
SD of NAA/Cr, Gray matter	22	.240	.057	12	.229	.054
Mean Cho/Cr, White matter	14	.325	.035	7	.333	.021
Mean Cho/Cr, Gray matter	14	.236	.034	7	.215	.021
SD of Cho/Cr, White matter	14	.045	.006	7	.061	.034
SD of Cho/Cr, Gray matter	14	.044	.012	7	.054	.025

Table 4

Hierarchical Multiple Regression Predicting Memory from Sex, Mean NAA/Cr, the Standard Deviation of NAA/Cr Among Gray Matter Voxels, the Standard Deviation of NAA/Cr Among White Matter Voxels, and the Interactions Between Sex and Each NAA/Cr Variable

Predictor	R^2	β	*t*	Sig
Step 1	.022			.410
Sex		.148	.836	.410
Step 2	.100			.551
Sex		.081	.422	.676
Mean NAA/Cr		-.118	-.589	.561
Standard deviation NAA/Cr, gray matter		-.244	-1.192	.243
Standard deviation NAA/Cr, white matter		.033	.159	.875
Step 3	.599			.001
Sex		.100	.730	.472
Mean NAA/Cr		2.108	4.603	.000
Standard deviation NAA/Cr, gray matter		.413	.931	.361
Standard deviation NAA/Cr, white matter		-1.255	-2.827	.009
Sex x Mean NAA/Cr		-2.311	-4.958	.000
Sex x Standard deviation NAA/Cr, gray matter		-.617	-1.314	.201
Sex x Standard deviation NAA/Cr, white matter		1.284	2.852	.009

Table 5

Regression of Memory on NAA/Cr measures, for Combined Sample and by Sex

	Both Sexes (n=33)			Males (n=22)			Females (n=11)		
	R^2	F	Sig	R^2	F	Sig	R^2	F	Sig
Entire model	.094	1.003	.406	.385		.030	.783		.010
Coefficients	β	t	Sig	β	t	Sig	β	t	Sig
(Constant)		47.673	.000		50.401	.000		36.939	.000
NAA/Cr mean	-.104	-.536	.596	.670	3.274	.004	-.780	-3.765	.007
NAA/Cr sd, white	-.268	-1.382	.177	.013	.068	.947	-.350	-1.626	.148
NAA/Cr sd, gray	.019	.019	.926	-.422	-2.017	.059	.422	2.072	.077

Table 6

Hierarchical Multiple Regression Predicting Speed from Sex, Mean NAA/Cr, the Standard Deviation of NAA/Cr Among Gray Matter Voxels, the Standard Deviation of NAA/Cr Among White Matter Voxels, and the Interactions Between Sex and Each NAA/Cr Variable

Predictor	R^2	β	*t*	Sig
Step 1	.035			.149
Sex		.254	1.487	.147
Step 2	.187			.039
Sex		.061	.355	.725
Mean NAA/Cr		-.019	-.112	.912
Standard deviation NAA/Cr, gray matter		-.455	-2.527	.017
Standard deviation NAA/Cr, white matter		-.101	-.553	.585
Step 3	.202			.068
Sex		.078	.450	.656
Mean NAA/Cr		.091	.161	.874
Standard deviation NAA/Cr, gray matter		-.074	-.130	.898
Standard deviation NAA/Cr, white matter		-1.040	-1.893	.070
Sex x Mean NAA/Cr		-.112	-.201	.842
Sex x Standard deviation NAA/Cr, gray matter		-.470	-.802	.430
Sex x Standard deviation NAA/Cr, white matter		1.027	1.837	.078

Table 7

Regression of Speed on NAA/Cr Measures, for Combined Sample and by Sex

	Both Sexes (n=34)			Males (n=22)			Females (n=12)		
	R^2	F	Sig	R^2	F	Sig	R^2	F	Sig
Entire model	.282	3.934	.018	.222	1.714	.200	.585	3.758	.060
Coefficients	β	t	Sig	β	t	Sig	β	t	Sig
(Constant)		55.043	.000		37.505	.000		38.244	.000
NAA/Cr mean	-.008	-.048	.962	.018	.077	.939	-.067	-.274	.791
NAA/Cr sd, whi	-.476	-2.832	.008	-.285	-1.327	.201	-.847	-3.288	.011
NAA/Cr sd, gray	-.111	-.628	.535	-.320	-1.360	.191	.412	1.556	.158

Table 8

Hierarchical Multiple Regression Predicting Memory from Sex, Mean Cho/Cr, the Standard Deviation of Cho/Cr Among Gray Matter Voxels, the Standard Deviation of Cho/Cr Among White Matter Voxels, and the Interactions Between Sex and Each Cho/Cr Variable

Predictor	R^2	β	*t*	Sig
Step 1	.061			.799
Sex		.061	.259	.799
Step 2	.623			.099
Sex		-.092	-.416	.683
Mean Cho/Cr		-.005	-.020	.984
Standard deviation Cho/Cr, gray matter		-.621	-2.627	.019
Standard deviation Cho/Cr, white matter		.539	2.228	.042
Step 3	.808			.037
Sex		-.563	-2.290	.041
Mean Cho/Cr		2.030	2.257	.043
Standard deviation Cho/Cr, gray matter		-.466	-2.178	.050
Standard deviation Cho/Cr, white matter		.351	1.638	.127
Sex x Mean Cho/Cr		-2.792	-2.655	.021
Sex x Standard deviation Cho/Cr, gray matter		.075	.190	.853
Sex x Standard deviation Cho/Cr, white matter		1.002	2.119	.056

Table 9

Hierarchical Multiple Regression Predicting Speed from Sex, Mean Cho/Cr, the Standard Deviation of Cho/Cr Among Gray Matter Voxels, the Standard Deviation of Cho/Cr Among White Matter Voxels, and the Interactions Between Sex and Each Cho/Cr Variable

Predictor	R^2	β	*t*	Sig
Step 1	.396			.075
Sex		.396	1.881	.075
Step 2	.579			.141
Sex		.178	.759	.459
Mean Cho/Cr		-.114	-.497	.626
Standard deviation Cho/Cr, gray matter		-.364	-1.463	.163
Standard deviation Cho/Cr, white matter		-.125	-.512	.615
Step 3	.611			.415
Sex		.088	.297	.771
Mean Cho/Cr		-.011	-.009	.993
Standard deviation Cho/Cr, gray matter		-.418	-1.498	.158
Standard deviation Cho/Cr, white matter		-.138	-.522	.610
Sex x Mean Cho/Cr		-.295	-.222	.828
Sex x Standard deviation Cho/Cr, gray matter		-.082	-.152	.881
Sex x Standard deviation Cho/Cr, white matter		.367	.729	.479

Table 10

Regression of Learning on NAA/Cr Measures, by Sex

	Males (n=18)			Females (n=6)		
	R^2	F	Sig	R^2	F	Sig
Entire model	.296	1.966	.166	.961	16.610	.057
Coefficients	β	t	Sig	β	t	Sig
(Constant)		29.050	.000		.804	.506
NAA/Cr mean	.580	2.375	.032	1.505	3.727	.065
NAA/Cr sd, white	-.132	-.573	.575	-1.888	-5.858	.028
NAA/Cr sd, gray	-.223	-.899	.384	-.132	-.577	.622

Table 11

Regression of Span on NAA/Cr Measures, by Sex

	Males (n=21)			Females (n=10)		
	R^2	F	Sig	R^2	F	Sig
Entire model	.339	2.908	.065	.591	3.373	.084
Coefficients	β	t	Sig	β	t	Sig
(Constant)		30.760	.000		31.464	.000
NAA/Cr mean	.414	1.832	.084	-.563	-1.981	.088
NAA/Cr sd, white	.285	1.338	.199	-.457	-1.546	.166
NAA/Cr sd, gray	-.536	-2.413	.027	.412	1.473	.184

Table 12

Regression of Digit Span Total on NAA/Cr measures, by Sex

	Males (n=21)			Females (n=11)		
	R^2	F	Sig	R^2	F	Sig
Entire model	.258	.405	.751	0.705	5.574	.029
Coefficients	β	t	Sig	β	t	Sig
(Constant)		22.401	.000		30.694	.000
NAA/Cr mean	-.198	-.736	.472	-.698	-2.892	.023
NAA/Cr sd, white	.196	.773	.450	-.345	-1.373	.212
NAA/Cr sd, gray	-.102	-.386	.704	.661	2.783	.027

Table 13

Regression of Spatial Span Backward on NAA/Cr measures, by Sex

	Males (n=21)			Females (n=11)		
	R^2	F	Sig	R^2	F	Sig
Entire model	.517	6.072	.005	0.195	.484	.705
Coefficients	β	t	Sig	β	t	Sig
(Constant)		22.574	.000		19.543	.000
NAA/Cr mean	.659	3.408	.003	.109	.286	.784
NAA/Cr sd, white	.216	1.182	.253	-.472	-1.173	.285
NAA/Cr sd, gray	-.596	-3.137	.006	.054	.136	.896