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***BDNF* val66met Polymorphism Affects Aging of Multiple Types of Memory**

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Abstract

The *BDNF* val66met polymorphism (rs6265) influences activity-dependent secretion of brain-derived neurotrophic factor in the synapse, which is crucial for learning and memory. Individuals homozygous or heterozygous for the met allele have lower *BDNF* secretion than val homozygotes and may be at risk for reduced declarative memory performance, but it remains unclear which types of declarative memory may be affected and how aging of memory across the lifespan is impacted by the *BDNF* val66met polymorphism. This cross-sectional study investigated the effects of *BDNF* polymorphism on multiple indices of memory (item, associative, prospective, subjective complaints) in a lifespan sample of 116 healthy adults aged 20–93 years. Advancing age showed a negative effect on item, associative and prospective memory, but not on subjective memory complaints. For item and prospective memory, there were significant age x *BDNF* group interactions, indicating the adverse effect of age on memory performance across the lifespan was much stronger in the *BDNF* met carriers than for the val homozygotes. *BDNF* met carriers also endorsed significantly greater subjective memory complaints, regardless of age, and showed a trend ($p < .07$) toward poorer associative memory performance compared to val homozygotes. These results suggest that genetic predisposition to the availability of brain-derived neurotrophic factor, by way of the *BDNF* val66met polymorphism, exerts an influence on multiple indices of episodic memory – in some cases in all individuals regardless of age (subjective memory and perhaps associative memory), in others as an exacerbation of age-related differences in memory across the lifespan (item and prospective memory).

Keywords

aging; *BDNF* val66met polymorphism; prospective memory; associative memory; subjective memory; episodic memory

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1. Introduction

Human memory can be classified into several different types, and each shows differential susceptibility to the effects of aging across the adult lifespan (Brickman & Stern, 2009; Craik & McDowd, 1987; Nilsson, 2003). For example, declarative, or episodic memory has been shown to decrease with increasing age (Verhaeghen, Marcoen, & Goossens, 1993), as opposed to procedural, or more nondeclarative types of memory (Light, 1991). Within the realm of declarative memory, there are further distinctions between memory types based upon the mnemonic process being utilized. Memory for items or lists, for example can be distinguished from memory for associations, the latter of which requires binding of at least two items, along with accompanying contextual information (Naveh-Benjamin, 2000; Old et al., 2008; Spencer & Raz, 1995). Both item memory and associative memory performance decrease with age (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2004). There has also been a recent surge of research interest in the ability to remember to do things in the future, referred to as prospective memory (Einstein & McDaniel, 1990). Prospective memory can be divided into two basic categories: time-based and event-based prospective memory cues. During time-based tasks, participants are asked to carry out tasks at a specific time in the future, and event-based tasks require the participant to respond to a particular environmental cue. Meta-analysis studies have indicated that both types of prospective memory decline with advancing age (Henry et al., 2004; Uttil, 2008). Finally, subjective assessment of one's own memory performance -- a kind of meta-memory -- has been referred to as subjective memory assessment or subjective memory complaints (Gilewski, Zelinski, & Schaie, 1990; McDonald-Miszczak, Hertzog, & Hultsch, 1995). Subjective memory has been studied in aging populations, with varied findings regarding its age-sensitivity (Hertzog & Pearman, in press; Pearman et al., 2014).

These age-sensitive aspects of human memory are so vulnerable to the aging process, putatively because they are served by brain systems whose components show a high rate of change with age (Buckner, 2004; Raz & Kennedy, 2009; Rodrigue & Kennedy, 2011). There is also, however great variability in individual memory performance, even within the aging process, and thus there is unexplained variance in memory performance that is due in large part to individual differences. One known aspect of such individual differences is genetic predisposition to different availability of neurotransmitter levels, neurotrophic factors and other neurobiological factors (Raz & Lustig, 2014).

Research focused on understanding factors that contribute to individual differences in memory ability has highlighted the fact that memory performance, like other cognitive abilities, is partly under genetic control (Payton, 2006). The study of candidate genes associated with cognitive and brain aging has been enabled by recent developments in assaying variants in specific genes, or single nucleotide polymorphisms (SNPs). One such candidate genetic polymorphism that is of special interest to the study of declarative memory is *BDNF* val66met, a valine to methionine substitution at codon 66 of the *BDNF* gene on chromosome 11 (Egan et al., 2003). The *BDNF* gene regulates activity-dependent secretion of brain-derived neurotrophic factor and met carriers of the *BDNF* gene show reduced secretion of this growth factor compared to val carriers. BDNF as a growth factor is crucial to learning and memory, likely through its regulation of LTP (long-term potentiation)

and LTD (long-term depression), and its role in synaptic plasticity, neuronal differentiation, proliferation of dendritic arbor, and axonal sprouting (Binder & Scharfman, 2004; Egan et al., 2003; Kojima et al., 2001; Murer et al., 2001). BDNF expression is fairly ubiquitous throughout the brain (Barbacid, 1994; Zhang et al., 2007), at least in rodents and primates, but by far the most research attention has been directed to BDNF expression in the hippocampus. Indeed, BDNF has been shown to be associated with altered hippocampal function (Egan et al., 2003; Dennis et al., 2011; Hariri et al., 2003) as well as decreased hippocampal volume (Bueller et al., 2006; Miyajima et al., 2008; Pezawas et al., 2004; Szeszko et al., 2005 but see Benjamin et al., 2010; Karnik et al., 2010), prefrontal cortex volume (Pezawas, et al. 2004), and integrity of the corpus callosum (Kennedy et al., 2009) all key components for optimal function of the declarative memory system (Buckner, 2004). Importantly, brain-derived neurotrophic factor production declines with age (Sohrabji & Lewis, 2006) and thus may be a salient neurobiological mechanism of age-related declines in declarative memory and in the changes observed in the structural and functional neural integrity of this memory system.

The *BDNF* val66met polymorphism has thus also been investigated for its association with declarative memory performance. While several studies have not shown an association between BDNF polymorphism and declarative memory measures (Benjamin et al., 2010; Gong et al., 2009; Houlihan et al., 2009; Karnik et al., 2010; Strauss et al., 2004; Tsai et al., 2008), several studies found that in samples of young adults, the *BDNF* met carriers had poorer verbal memory for items than the *BDNF* val homozygotes (Dempster et al., 2005; Egan et al., 2003; Hariri et al., 2003; Ho et al., 2006; Tan et al., 2005). Recent meta-analyses indicate that most of these studies relied mainly on tasks of item memory, and almost exclusively tested verbal memory (Kambietz et al., 2012; Mandelmann & Grigorenko, 2012). Furthermore, studies of BDNF and memory in healthy aging populations are rare. In studies limited to only older adults, Harris et al., (2006) found no effect of *BDNF* val66met on memory, whereas in a sample of elderly individuals, Miyajima et al., (2008) found an association of poorer delayed verbal recall in met homozygotes. In another cohort of older adults, Laing et al., (2012) reported weak or null findings between *BDNF* val66met polymorphism and verbal memory.

Very few studies have examined the association of *BDNF* val66met polymorphism in memory indices outside of verbal item memory or in a sample that spans the adult lifespan. Previously in a separate lifespan sample, we reported a significant relationship between *BDNF* val66met polymorphism and associative memory, with *BDNF* met carriers performing more poorly than val homozygotes (Raz et al., 2009) and that *BDNF* polymorphism effects were synergistically exacerbated by increased blood glucose levels (Raz et al., 2008). In a group of young adults, Yogeetha et al. (2013) did assess multiple types of memory, but found only an influence of *BDNF* group on visuo-spatial memory: on one test met carriers performed better and on the other test val carriers performed better. To date, no significant associations have been reported for subjective memory assessments and *BDNF* genotype in any age population.

To further our knowledge of the role of the *BDNF* polymorphism on the normal aging of multiple types of human memory, the current study investigated the effects of *BDNF*

val66met single nucleotide polymorphism on individual differences in declarative memory performance in a healthy adult lifespan sample of aging. We examined the modifying effect of *BDNF* polymorphism on four specific types of memory -- item memory (California Verbal Learning Test; CVLT), associative memory (Woodcock-Johnson Battery Memory for Names subscale), prospective memory (Memory for Intentions Test), and subjective memory complaints (Memory Functioning Questionnaire; MFQ). We hypothesized that individuals with a genetic predisposition to lower secretion of brain-derived neurotrophic factor (the *BDNF* met carriers) would show poorer memory performance with age than their counterparts having predisposition to greater secretion of BDNF (the *BDNF* val homozygotes) across all four types of memory tasks.

2. Results

2.1. Sample Characteristics

Participants included 116 individuals (64 women, 52 men) for whom complete cognitive and genetic data were available. Participants ranged in age from 20-93 (mean 55.8 ± 17.4 years) with about college-level education (mean 15.5 ± 2.6 years), high MMSE (Mini Mental State Examination) scores (mean 28.9 ± 1.04), and low CESD (Center for Epidemiologic Study - Depression) scores (4.36 ± 3.93), suggesting that the participants were not evidencing signs of dementia or depression.

The allelic distribution of the *BDNF* val66met polymorphism fit the Hardy-Weinberg equilibrium ($\chi^2 = 1.6$, $p = .82$), with 68% of participants being val homozygotes ($n = 79$), and 27% val/met heterozygotes ($n = 31$), whereas 6 participants had the rare met/met genotype (5%). To avoid uneven group sizes we collapsed across the val/met and met/met groups to form a heterozygous/homozygous met group, therefore the sample consisted of 79 *BDNF* val individuals and 37 *BDNF* met individuals. The val and the met individuals did not differ significantly in age ($p = .38$), education level ($p = .59$), MMSE ($p = .72$), CESD ($p = .07$) or sex distribution ($p = .17$). Sample demographic information is presented in Table 1.

2.2. Effect of Age and *BDNF* val66met Polymorphism on Memory

For each memory index we conducted general linear model analysis with the memory score as a continuous dependent variable and age (continuous), *BDNF* group (2 level category: val homozygote or met hetero-/homo-zygote) and their interaction as predictors. When the interaction term was not significant ($p > .15$) it was removed from the model and re-estimated to conserve statistical power. Decomposition of significant Age x *BDNF* interactions was accomplished by examining age and memory correlations in each of the *BDNF* groups to note the nature of the interaction. Detailed descriptions of the indices used for each measure of memory are provided in the Method section 4.3.

2.2.1. Item memory—We measured several indices of memory from the CVLT to investigate item memory. We computed multiple measures for four categories of memory performance: immediate recall, delayed recall, learning strategies, and delayed recognition.

For immediate recall measures of item memory we examined CVLT Trial 1, Trial 5, and Total Trials. We found decreasing memory performance with age on all three measures

[$F(1, 113)=16.49, p < .001$; $F(1, 112)= 13.38, p < .001$; and $F(1, 112)=27.84, p < .001$, respectively]. We found marginally better memory performance in the *BDNF* val group on CVLT Trial 5 [$F(1, 112)= 3.69, p = .06$] and Total Trials [$F(1, 112)=3.14, p = .08$], but not on Trial 1 [$p > .20$]. However, these main effects were qualified by significant age x *BDNF* interactions: Trial 5 [$F(1, 112)=4.58, p < .05$] and Total Trials [$F(1, 112)= 4.22, p < .05$]. Decomposition of these interactions revealed that the *BDNF* met group showed a higher association between age and memory ($r = -.54$; $r = -.62$) than the *BDNF* val group ($r = -.16$; $r = -.32$) on Trial 5 and Total Trials, respectively, indicating that the effect of aging on item memory depends on *BDNF* group (see Figure 1A, B). These models for Trial 1, Trial 5, and Total Trials accounted for 14%, 11%, and 21% of the variance in those measures, respectively.

For delayed recall of items we measured delayed free recall and delayed cued recall. We found significant main effects of age for both free recall [$F(1, 112)=14.12, p < .001$] and cued recall [$F(1, 112)=12.20, p = .001$]. We also found significant main effects of *BDNF* group for both free [$F(1, 112)=4.61, p < .04$] and cued recall [$F(1, 112)=5.09, p < .03$]. However both of these effects were qualified by age x *BDNF* interactions [free: $F(1, 112)=5.80, p < .02$; cued: $F(1, 112)=5.13, p < .03$]. Breakdown of these interactions revealed that the aging and memory association is greater in the *BDNF* met group (free: $r = -.58$; cued: $r = -.58$), than in the *BDNF* val group (free: $r = -.14$; cued: $r = -.12$) indicating that the effects of aging on delayed item memory are dependent upon *BDNF* group membership (see Figure 1C, D). These models accounted for 12% of the variance in delayed free recall and 10% of the variance in delayed cued recall.

For the strategy learning based memory measures, semantic clustering and serial clustering, we found that semantic clustering was adversely affected by aging [$F(1, 112)=6.51, p = .01$] whereas serial clustering was not [$p = .24$]. Both strategies were affected by *BDNF* polymorphism: semantic $F(1, 112)=4.74, p < .04$, serial $F(1, 112)= 4.70, p < .04$. Furthermore, for both semantic [$F(1, 112)=5.96, p < .02$] and serial [$F(1, 112)=5.95, p < .02$] clustering there were significant age x *BDNF* interactions. The *BDNF* met group showed decreased semantic clustering with age ($r = -.45$) whereas the *BDNF* val group did not ($r = -.01$). For serial clustering, the interaction was due to no age effect on this strategy in the *BDNF* val group ($r = -.14$), but a significant increase in the use of this strategy in the *BDNF* met group ($r = .33$). See Figure 1E and F. The models for semantic and for serial clustering accounted for 8% and 5% of the variance in semantic and serial memory strategies, respectively.

For delayed recognition memory we computed hits, false positives, and d' (a measure of discriminability of items). There was a significant adverse effect of age on hits [$F(1, 112)=5.49, p < .02$], false positives [$F(1, 113)=9.40, p = .003$], and d' [$F(1, 112)=14.00, p < .001$], but only a significant effect of *BDNF* on hits [$F(1, 112)= 9.66, p = .002$] and d' [$F(1, 112)=5.43, p < .03$]. However, both of these measures of recognition were qualified by significant age x *BDNF* interactions [hits: $F(1, 112)=9.91, p = .002$ and d' : $F(1, 112)=6.03, p = .02$]. The aging and memory association was significant in the *BDNF* met group (hits: $r = -.47$; d' : $r = -.58$) but not in the *BDNF* val group (hits: $r = .09$; d' : $r = -.13$). See Figure 1G

and F. These models accounted for 9% of the variance in hits, 8% in false positives, and 12% in d' .

2.2.2. Associative Memory—We investigated two measures of associative memory: memory for names immediate and delayed. For the immediate memory we found a significant main effect of age [$F(1, 113)=36.03, p < .001$] with decreased memory performance with aging. We also found a marginally significant main effect of *BDNF* [$F(1, 113)= 3.44, p = .07$] with individuals in the *BDNF* met group displaying poorer memory (see Figure 2A). There was no significant age x *BDNF* interaction. This model accounted for 27% of the variance in immediate associative memory.

For the delayed memory measure we found a significant effect of age [$F(1, 113)= 38.02, p < .001$] where memory decreased with increasing age. There was also a trend toward individuals in the *BDNF* met group showing poorer memory (see Figure 2B), but this effect of *BDNF* on delayed associative memory did not reach statistical significance [$F(1, 113)= 2.63, p = .11$]. The age x *BDNF* interaction was not significant. This model accounted for 27% of the variance in delayed associative memory.

2.2.3. Prospective Memory—We investigated three indices from the MIST prospective memory test: time-based and event-based prospective memory, and retrospective memory. For the time-based prospective memory tasks we found significant main effects of age [$F(1, 112)= 35.58, p < .001$] and not *BDNF* group [$F(1, 112)= 4.17, p = .12$], but these were qualified by a significant age x *BDNF* interaction [$F(1, 112)= 5.01, p < .03$]. Decomposition of the interaction revealed that the association between time-based tasks and age was weaker in the *BDNF* val group ($r = -.40$), whereas for the *BDNF* met carriers the age association was stronger ($r = -.58$), indicating that the effect of aging on time-based prospective memory depends on the individual's *BDNF* genotype (see Figure 3A). The model accounted for 27% of the variance in time-cued prospective memory.

For event-based prospective memory tasks we found significant main effects of age [$F(1, 112)= 11.84, p = .001$], *BDNF* group [$F(1, 112)= 5.12, p < .03$], and also a significant age x *BDNF* interaction [$F(1, 112)= 6.45, p < .02$]. *BDNF* val carriers showed a weaker age effect ($r = -.11$) than *BDNF* met carriers ($r = -.46$), again indicating that the effect of age on event-based prospective memory depends on *BDNF* genotype (see Figure 3B). Note that most participants did very well on event-cued memory, however, compared to time-cued memory tasks. This model accounted for 11% of the variance in event-based prospective memory scores.

For the retrospective memory score we found a main effect of age [$F(1, 112)= 26.72, p < .001$] as well as a main effect of *BDNF* [$F(1, 112)= 4.78, p < .04$]. Individuals in the *BDNF* met group showed poorer memory performance than the *BDNF* val group (see Figure 3C). The age x *BDNF* interaction was not significant. This model accounted for 23% of the variance in retrospective memory scores.

2.2.4. Subjective Memory—We used the Memory Functioning Questionnaire to examine subjective memory complaints. We found no significant age differences in subjective

memory complaints ($F < 1$), but we found a significant main effect of *BDNF* group [$F(1,113) = 4.41, p < .04$], with individuals in the *BDNF* met group endorsing greater forgetting complaints than those in the *BDNF* val group (see Figure 4). There was no significant age x *BDNF* interaction. The model accounted for 4% of the variance in subjective memory complaints.

3. Discussion

In this study we investigated the effects of the *BDNF* val66met polymorphism in a healthy adult lifespan sample on aging of multiple types of memory: item memory, associative memory, prospective memory, and subjective memory complaints. We found both significant aging and *BDNF* polymorphism main effects on memory, as well as *BDNF* by age interactions on memory, suggesting that for some types of memory *BDNF* has an effect on individuals of all ages, whereas on other types of memory, the detrimental effects of aging on memory depend on an individual's *BDNF* genotype. We discuss the specific effects of *BDNF* on memory performance by memory type below.

3.1. Item Memory

Across the various indices of item memory performance on the CVLT, we found reliable age by *BDNF* polymorphism interactions, suggesting that age-related memory differences among individuals with the val/val genotype are milder than those for individuals who are met carriers. The scatterplots in Figure 1, taken together suggest that for individuals with high expression of brain-derived neurotrophic factor (val homozygotes), the effect of age on verbal item memory is essentially null. However, the group of individuals with lowered *BDNF* expression shows a significant decline in item memory with advancing age. This is true for the number of words individuals were able to recall immediately after presentation as well as after a half hour delay and for both free recall and cued recall, memory indices that traditionally show large aging effects (Craik & McDowd, 1987).

We also observed that item memory discrimination (d') was reduced sharply with age in the *BDNF* met carriers, but was unaffected in the val homozygotes, and that this effect seemed to stem from a decrease in correct hits, rather than an increase in false positives. These *BDNF* polymorphism results are in line with previous research (Goldberg et al., 2008). Though, in that study, the authors interpreted this finding as specificity of the role of *BDNF* in hippocampal-based memory encoding processes, as opposed to the suspected role of extra-hippocampal cortical regions involvement in recollection or familiarity (Goldberg et al., 2008; Henson, Hornberger, & Rugg, 2005). However, in our study we also find effects of *BDNF* on aspects of memory that are thought to be extra-hippocampal, such as semantic and serial clustering strategy selection, that utilize control regions of the brain, such as dorsolateral prefrontal cortices, suggesting that the influence of *BDNF* polymorphism is not limited to hippocampal processes of memory.

Indeed, our participants in the different *BDNF* groups differed significantly in their use of mnemonic strategies. On the CVLT individuals can adopt a semantic clustering strategy, in which they group items from a list of words by category to help memorization (semantic clustering) or they can adapt a less elaborate strategy of attempting to memorize the items in

the order in which they were presented (serial clustering). Advancing age generally brings about a shift from semantic clustering strategy to a serial clustering strategy (Kirchhoff, Gordon, & Head, 2014). Here we demonstrate that there is no age-related loss of semantic clustering use in the *BDNF* val homozygotes, but a significant loss of this strategy in the met carriers. Similarly, while there is no significant age difference in the use of serial clustering in the val/val group, the met carriers show a significant age-related increase in the adoption of this less elaborate mnemonic strategy. This intriguing finding suggests that individuals with decreased expression of brain-derived neurotrophic factor not only show poorer memory compared to the val/val group, but also demonstrate less desirable selection of self-initiated strategy use. Strategy selection on the CVLT has been shown to be sensitive to dorsolateral prefrontal cortex volume (Kirchhoff, Gordon, & Head, 2014) suggesting that the effects of *BDNF* on these measures of item memory may not be entirely hippocampal-driven. Furthermore, other researchers have shown that *BDNF* also effects spatial navigation strategy use (Banner et al., 2011), which is also extra-hippocampal in nature, lending support to the idea that *BDNF*'s role involves regions of the brain outside of the hippocampus. In all, we report that knowing one's age and *BDNF* val66met genotype allows for explaining up to 21% of the variance in verbal item memory performance.

3.2. Associative Memory

In contrast to the strong findings for *BDNF* on age-related differences in item memory, we find that regardless of age, met carriers performed more poorly on both immediate and delayed recognition of name-face pairs, but neither of these surpassed trend level significance (Figure 2). It remains unclear why item memory would show stronger associations with *BDNF* than associative memory does, or why the item memory associations with *BDNF* genotype were dependent on age and the associative memory effects were found as main effects, regardless of age. One possibility for this weaker finding is that the effects of aging on this associative memory task are particularly pronounced, and stronger than even the item memory age-associations. This could be due to several reasons including differential difficulty of the two tasks (associative memory is more difficult than item memory), the processes of encoding/retrieval required between the two tasks (item memory requires rehearsal/retrieval of one item as a member of a list, whereas associative memory requires binding of items together at encoding and retrieval of not only the items but of their relation as well), as well as the strategies available to aid in these mnemonic processes (i.e., chunking vs serial order learning), or the modality in which the two tasks are presented (the item memory task was verbal, whereas the associative memory task involved nonsense names paired with drawings of novel space creatures).

In the associative memory task (Woodcock-Johnson Memory for Names test), participants must learn across 72 trials the pairing of a nonsense name with a novel drawing of a space creature and then half an hour later perform a recognition test for this paired learning. Participants report that this is quite a difficult task and indeed, the age effects across the lifespan are steep (Raz et al., 2008; 2009). Associative memory requires the successful binding of multiple items and their context, and performance significantly decreases with age as compared to item memory (Spencer & Raz, 1995; Old et al., 2008; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003). Such impairments in associative memory have been

demonstrated across multiple tasks including item and location pairs (Chalfonte & Johnson, 1996), face-name pairs (Naveh-Benjamin, 2004), word pairs (Bender, Naveh-Benjamin, & Raz, 2010), and item-color pairs (Bastin et al., 2013). These deficits may occur from a lack of ability to bind items together into a coherent unit of information at encoding (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000), from recollection impairments at retrieval (Light et al., 2000; Cohn et al., 2008), or both. Additionally, associative memory deficits are most pronounced when items are difficult to encode (i.e., non-words; Naveh-Benjamin, 2000), or when pairs seem unrelated (i.e., when participants must create novel associations between items; Old et al., 2008) and both instances are applicable to the task used in the current study. In such cases, memory deficits seem to be related to the creation of associations between differing items rather than the creation and retrieval of associations between item and context (Old et al., 2008). Thus, we replicate here the findings of strong age effects on associative memory (Raz et al., 2008; 2009, and also that *BDNF* met carriers perform worse than val homozygotes on both immediate and delayed recognition, although in this sample the effects were only at trend level. Knowing age and *BDNF* status explains up to 27% of the variance in those two measures of memory.

3.3. Prospective Memory

There is a growing interest in the relationship between prospective memory and aging. Prospective memory is the memory for intentions; an action a person needs to “remember to remember” to perform in the future (Einstein & McDaniel, 1990; Gonneaud et al., 2014; Graf & Utzl, 2001). Studies generally examine prospective memory both for time-based and event-based cues and the effect each type of cue has on performance (Henry et al., 2004) as well as a retrospective memory test of the assessment. During time-based tasks, participants are asked to carry out tasks at a specific time in the future, and event-based tasks require the participant to respond to a particular environmental cue administered by the tester (Henry et al., 2004; Einstein et al., 1995). The existing literature on prospective memory and aging has revealed mixed results, however (McDaniel & Einstein, 2008). For example, many studies that have employed prospective memory tasks have reported a decline in performance in older participants (Henry et al., 2004), while others have indicated performance does not necessarily worsen with age (Einstein et al., 1995). Furthermore, these contrasts have been found at the level of the task: some studies show a “typically pronounced” age-related decline of prospective memory for time-based tasks (Henry et al., 2004; Einstein et al., 1995), but other studies have revealed better performance with age on the same type of task (Henry et al., 2004).

In the current study, we report significant negative effects of age across the adult lifespan on both time-cued and event-cued prospective memory tasks (Figure 3A-B) and inspection of those scatterplots suggests that time-cued tasks are more difficult than event-cued tasks. Retrospective memory for these tasks is also lowered as age progresses. However, we find significant interactive effects of age and *BDNF* group on prospective memory, where the aging slope for the met carriers is worsened compared to the shallower age slope of the val homozygotes, suggesting that lesser availability of brain-derived neurotrophic factor exacerbates the effects of age on prospective memory. Being in the met risk-group, however, has an adverse effect on retrospective memory performance regardless of one's

age. The only other study to examine the association between *BDNF* val66met polymorphism and prospective memory (Yogeetha et al., 2013) perhaps failed to find an association because they only examined younger individuals in their sample and would not have been able to test for this age x *BDNF* interaction. Indeed, knowing an individual's age and *BDNF* status allowed us to explain 27%, 11% and 23% of the variance in prospective time-cued, event-cued, and retrospective memory tasks, respectively.

3.4. Subjective Memory Assessment

As with prospective memory, there has been recent resurgence of interest in an individual's self-assessment of his or her memory ability. Some studies find that self-assessments of memory complaint endorsement increase with age (Bolla, et al., 1991), while others do not (Pearman & Storandt, 2004), and that these subjective assessments may correlate with actual memory performance in some cases (Lane & Zelinski, 2003; Levy-Cushman & Abeles, 1998; Mascherek & Zimprich, 2011; McDonald-Miszczak, et al., 1995; Parisi et al., 2011; Zelinski, Gilewski, & Anthony-Bergstone, 1990), but not others (Pearman, Gerstorf, & Hertzog 2014; Poitrenaud, Malbezin, & Guez 1989; for review see Hertzog & Pearman, in press). We were interested in whether the polymorphism that affects memory performance would also have an effect on subjective reports of memory ability. Using the Memory Functioning Questionnaire (Gilewski, Zelinski, & Schaie, 1990), we found that individuals who were carriers of the *BDNF* met allele reported more subjective memory complaints than those in the val homozygous group, regardless of age. In fact, with *BDNF* accounted for, we saw no age-related differences in subjective memory in our healthy lifespan sample. Instead, subjective memory complaints depended on one's *BDNF* polymorphism group, although these effects were modest, explaining only 4% of the variance in subjective memory reports.

Again, it is interesting to speculate about the possible mechanisms underlying these results. Subjective memory assessments appear to rely not only on the same processes or brain regions involved in the actual memory processes, e.g., hippocampal (Cherbuin et al, 2014; Erk et al., 2011; Hafkemeijer et al., 2013; Saykin et al., 2006; Scheef et al., 2012; Stewart et al., 2011; van der Flier, et al., 2004) or entorhinal cortex (Jessen et al., 2006) structure or function, but subjective memory assessment also likely relies on a more cortical network of brain regions, including at least the prefrontal cortex and precuneus (Erk et al., 2011; Hafkemeijer et al., 2013; Rodda et al., 2009; Saykin et al., 2006; Scheef et al., 2012; Stewart et al., 2011). These subjective memory assessment results, coupled with our memory strategy selection findings, lend further support for the view that *BDNF* does not only exerts effects via activity-dependent expression in hippocampal synapses, but also in extra-hippocampal, though memory-relevant regions such as the prefrontal cortex.

3.5. Summary and General Discussion

In this study we have shown that genetic predisposition to availability of brain-derived neurotrophic factor, by way of the *BDNF* val66met polymorphism, is related to memory performance across several types of memory tasks – item memory for verbal information, associative memory for names and faces (albeit weaker), time-cued and event-cued prospective memory, and subjective memory assessment. Given the varied, wide-ranging set of processes underlying these different types of memory, and the network of brain regions

that serve them, these findings suggest that the neurobiological role that BDNF plays in memory is fundamental and generalized, underlying both hippocampal-driven and extra-hippocampal/cortical mechanisms of BDNF at the synapse. Furthermore, met carriers even have shorter iconic visual memory than val carriers (Beste et al., 2011) suggesting that BDNF may have its effects as early as the pre-attentive stages of memory.

The precise neurobiological mechanisms of BDNF's role in memory remains incompletely understood, but the *BDNF* polymorphism seems to have more widespread effects in the brain beyond regulation of activity-dependent secretion of the neurotrophin in the hippocampus. Most *in vitro* studies of BDNF function are conducted in the hippocampus, likely biasing thought toward that region. Indeed, hippocampal neurons locally and rapidly release BDNF into the synapse in an activity-dependent manner (Kojima et al., 2001), suggesting that hippocampal plasticity is a possible mechanism for the genetic effects seen in memory. In mice, the *BDNF* val66met polymorphism impairs NMDA receptor-dependent plasticity in the hippocampus (Ninan et al., 2010). Spectroscopy studies find that BDNF prodomain induces structural changes such as inducing neural growth cone retraction in hippocampal neurons (Anastasia et al., 2013) and that *BDNF* met carriers evidence altered NAA and glutamate metabolic ratios in the hippocampus compared with val/val homozygotes (Gruber et al., 2012). BDNF influences synaptic neuronal plasticity in the hippocampus and is important for the survival of neurons or perhaps even the replacement of neurons via neurogenesis to aid in forgetting (Frankland, Köhler, & Josselyn, 2013).

Examination of BDNF function in extra-hippocampal regions is less common to date. Memory acquisition is associated with an increase in expression of BDNF mRNA and TrkB activation in several brain areas (Yamada & Nabeshima, 2004 for review). Since met carriers have a genetic predisposition to decreased BDNF secretion, poorer memory might be in part due to decreased expression of BDNF mRNA and TrkB activation throughout the brain. In primates, BDNF is expressed most intensely in layers III and V of the cerebral cortex, substantia nigra, caudate and putamen, as well as CA3 and the granular cell layer of the hippocampus (Zhang, et al., 2007), and moderately expressed in layers II and IV of the cerebral cortex, cerebellar, midbrain and brainstem nuclei, and CA2 and CA4 of the hippocampus. If the *BDNF* val66 polymorphism equally decreases expression in these regions in an equivalent fashion, memory performance decrements could be a reflection of decreased expression in any or all of these extra-hippocampal regions.

Another memory-relevant region, the prefrontal cortex has also been shown to have high expression of BDNF, and prefrontal cortex volume and activation have been shown to differ in BDNF val and met carriers (Pezawas et al., 2004; Schofield et al., 2009). In the current study, we find BDNF to be associated with not only traditional "hippocampal" aspects of memory, but also with more prefrontal-dependent processes such as strategy selection and subjective memory assessments. These findings suggest that BDNF's mechanism may not be limited to the traditionally thought role of synaptic effects in the hippocampus, but rather may also have its effects synaptically in extra-hippocampal, cortical regions, such as the prefrontal cortex. In fact, relational binding necessary for associative memory has been shown to be a highly hippocampal-dependent process (e.g., Giovanello, Schnyer, & Verfaellie, 2004; Sperling et al., 2003), but in our study showed the weakest association

with BDNF polymorphism of all the tasks examined, suggesting a broader role of BDNF outside of the hippocampal formation. Interestingly, *BDNF* val and met carriers differ in their response to TCDS (transcranial doppler stimulation) and TMS (transcranial magnetic stimulation) of motor cortex, suggesting a differential susceptibility of synapses undergoing LTP/LTD based on genotype (Cheeran et al., 2008). Notably, BDNF also regulates slow wave oscillations during sleep (Bachmann et al., 2012; Mascetti et al., 2013), and sleep is an important component of memory consolidation (Tononi & Cirelli, 2014) and might provide another window into BDNF's effects on memory. Disturbances in the synapse likely are to blame for poorer memory, in part regulated by BDNF, and indeed, BDNF synaptic repair has been suggested as a disease-modifying strategy for neurodegenerative diseases such as AD (Lu et al., 2013) and may be accomplished through aerobic exercise intervention (Erikson et al., 2012; 2013).

These results should be interpreted within the context of their limitations and strengths. Cross-sectional designs by definition cannot assess within-person change over time; rather they can estimate, based on measurement of individuals of all ages, how the aging process may proceed. Holding individual differences constant with a repeated measures design is the ideal investigation of true aging effects and future studies should examine the longitudinal effects of aging on memory changes in *BDNF* val and met groups. A strength of this cross-sectional design, however is the sampling from the whole adult lifespan, rather than using the more common, but limited extreme age group comparison approach, which cannot explore age trajectories across the lifespan, nor can examine linear age x genotype interactions. Second, several studies have found that *BDNF* val66met polymorphism also exerts effects on domains of cognition besides memory: reasoning (Harris et al., 2006), executive functions (Erikson et al., 2008), task-switching (Gajewski et al., 2011), attention (Getzmann et al., 2013), and processing speed (Ghisletta et al., 2014; Raz et al., 2009). Thus, the effect of BDNF is likely not selective to memory, *per se*, but impacts other cognitive processes, that may in turn relate to memory processes. Future studies should compare multiple types of memory along with these other domains of cognition to examine their interrelation with *BDNF* influence. Third, while neural mechanisms may be inferred or speculated from genetic polymorphisms, future studies should examine neuroanatomical substrates as potential “mediators” of BDNF's effects on memory, such as hippocampal volume or white matter structural connectivity. These studies are underway in our lab currently. Last, candidate gene association studies are often potentially underpowered to find effects on brain or cognitive variables, including the current study. This is a pervasive issue in that, on the one hand, very large epidemiological studies would be ideal for characterizing the genotype of a sample; on the other hand, more manageable sample sizes are required to be able to administer controlled, high-quality neuropsychological, cognitive, and neuroimaging tests to individuals who are screened to represent a “normal, healthy” population. For this reason, replication studies are highly important. Future studies that have adequate power should also examine the interactive or additive nature of multiple SNPs on one another (e.g., *BDNF* +/- *APOE*; Kauppi et al., 2014; Laukka et al., 2013; Ward et al., 2014).

4. Experimental Procedure

4.1. Participants

The sample consisted of 116 volunteers from the metro area who were recruited from flyers and media advertisements and were paid for their time. Participants were healthy individuals screened against history of cardiovascular (except for controlled essential hypertension), neurological, psychiatric, and metabolic disease, head trauma with loss of consciousness, alcohol and drug abuse, diabetes, thyroid problems, cancer, as well as cognitive-altering medications. Participants were screened for dementia and depression with the MMSE (Folstein et al., 1975) and the Center for Epidemiological Study Depression Scale (CESD; Radloff, 1977), with cut-offs of 26 and 15, respectively. All participants were strongly right-handed (75% and above on the Edinburgh Handedness Questionnaire; Oldfield, 1971). Participants underwent vision and hearing screening evaluation before entering study. All participants provided written informed consent in accordance with the university institutional review board guidelines.

4.2. DNA Genotyping

DNA extraction and genotyping assays were conducted at the University of Texas Southwestern Medical Center Microarray Core Facility. For genotyping quality control, 10% direct repeats and DNA sequencing for verification were performed. We used both control DNA and no-template controls and ran all 5'-nuclease assays using Applied Biosystem's 7900HT Fast Real-Time PCR System. DNA was extracted from saliva samples using the prepIT-L2P purifier reagent (DNA Genotek, Ottawa, ON, Canada) and following the procedure in the manual purification protocol handbook. DNA integrity was determined by subjecting the samples to electrophoresis with 1% agarose gels. Polymorphism for *BDNF* val66met (rs6265) was ascertained using Taqman SNP Genotyping assays (Applied Biosystems) with DNA sequencing reactions carried out using the 0.5X protocol for ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems).

4.3. Memory Tasks

4.3.1 California Verbal Learning Test, 2nd Ed. (CVLT-II)—The CVLT (Delis, Kramer, Kaplan, & Ober, 2000) is a measure of verbal learning of items in lists. Participants are orally presented a list of 16 words, which fall into four categories: transportation, vegetables, furniture, and animals. The list is initially presented five times with participants recalling as many words as they can between each presentation. Participants are then tested on their ability to remember the words after a short (less than five minutes) and long delay (20-30 minutes). During the short delay participants hear a second list of words, which includes words from overlapping and novel categories, and are asked to recall them. After both the short and long delay they are asked to recall the original list through free recall and category cued recall. After the long delay there is a recognition task of the first list with both novel words and words from the second list as distractors. Participant scores are based on correct responses during learning, immediate, and delayed recall as well as learning strategy (semantic clustering into categories or serial learning of the items in the list) and *d'* (a measure of item discriminability based on hits vs false positives). We utilized the CVLT-II Comprehensive Scoring System to obtain memory measures from four categories of

mnemonic ability: immediate recall (Trial 1, Trial 5, Total Trials), delayed recall (long free recall, long cued recall), learning strategies (semantic clustering, serial clustering), and delayed recognition (hits, false positives, d').

4.3.2. Woodcock Johnson III (WJ-III) Memory for Names (MfN)—The Memory for Names Subscale of the WJ-III (Mather, 2001; Woodcock et al., 2003) is a measure of associative memory. This task requires participants to learn the names of twelve space creature drawings, each with unique features and a novel but nonsensical name (e.g., Jawf, Meegoy). During a learning/recognition phase a drawing is presented, paired orally with the name, and the participant has to find it within a group of other space creatures while remembering previous stimuli. With each successive trial the memory load increases until all 12 space creatures are presented. After a 30-40 minute delay the participant is asked to point to the space creature named orally by the experimenter. After each selection, a new array of space creatures is presented to avoid the use of the process of elimination. We obtain two indices of performance on this test: immediate and delayed recognition.

4.3.3. Memory for Intentions Test (MIST)—The MIST (Raskin, Buckheit, & Sherrod 2010) is a measure of prospective memory. The test consists of eight time-delayed prospective memory tasks performed while the participant is busy working on a task (word search). Each task includes a delay between encoding and retrieval. No explicit prompt is given when the occasion to act occurs. Trials vary by cue type (time vs. event), time delay (long vs. short), and response type (action vs. verbal). Five types of errors can be analyzed: prospective memory failure errors, task substitution errors, loss of content errors, loss of time errors, and random errors. To evaluate retrospective memory functioning, a series of multiple-choice recognition items is given at the end of the testing session that query the participant on the specific tasks that were presented during the test. We use three indices of performance on this test: time-based prospective memory, event-based prospective memory, and retrospective memory.

4.3.4. Memory Functioning Questionnaire (MFQ)—The MFQ (Gilewski, Zelinski, & Schaie, 1990; Revell, Caskie, Willis, & Schaie, 2001) is an index of subjective memory complaints. Participants indicate by Likert scale how often they have problems remembering different kinds of information such as faces, phone numbers, or maintaining train of thought (e.g., when reading a novel), how serious these problems are when they occur, and how present memory performance compares to past time periods. Each is answered on a 7-point Likert scale with 1 indicating poorer memory performance/more problems and 7 indicating better memory performance/less memory problems. Thus, higher scores indicate better memory/fewer subjective memory endorsements. All questions on the MFQ pertaining to subjective memory complaints (i.e., sections 1-7, excluding section 8 which assesses mnemonic strategies) were summed to yield a total subjective memory score, which could range from 57 to 399.

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Highlights

- *BDNF* val66met single nucleotide polymorphism regulates brain-derived neurotrophic factor
- Carriers of 66met allele show reduced BDNF secretion compared to val homozygotes
- *BDNF* expression and secretion is crucial for learning and memory in the synapse
- *BDNF* met carriers showed poorer memory than val/val on four different types of memory
- Differential aging trajectories for memory across lifespan depending on *BDNF* group

Figure 1.

The effects of aging on item memory depend on *BDNF* val66met polymorphism, with individuals in the *BDNF* met group showing poorer memory with increased age. Panels A-H illustrate this finding across several indices of item memory on the CVLT, representing immediate and delayed recall, strategy selection, and recognition indices.

Figure 2.

The effect of *BDNF* val66met polymorphism on immediate (A) and delayed (B) associative memory for name-face pairs from the WJ-III test. Individuals in the *BDNF* met group had poorer memory scores, regardless of age, although these effects were at trend level.

Figure 3.

The effects of *BDNF* val66met polymorphism on a test of prospective memory, the MIST. Panel A illustrates that the association between time-cued prospective memory and age was weaker in the *BDNF* val group than for the *BDNF* met carriers. Panel B illustrates that the association between time-cued prospective memory and age was weaker in the *BDNF* val group than for the *BDNF* met carriers. Panel C depicts the main effect of *BDNF* group on a retrospective measure of memory from the same test: individuals in the *BDNF* met group had poorer memory than individuals homozygous for *BDNF* val.

Figure 4.

The effects of *BDNF* val66met polymorphism on subjective memory complaints from the Memory Functioning Questionnaire. Individuals in the *BDNF* val group had fewer subjective memory complaints than members of the *BDNF* met group, regardless of age.

Table 1

Sample demographic information by *BDNF* genotype and total sample: mean $\pm$ SD

Group	N	Age	Edu	MMSE	CES-D	% Women
val/val	79	54.81 $\pm$ 18.01	15.39 $\pm$ 2.53	28.89 $\pm$ 1.05	4.81 $\pm$ 4.20	59
any met	37	57.84 $\pm$ 16.19	15.68 $\pm$ 2.73	28.81 $\pm$ 1.02	3.41 $\pm$ 3.14	46
Total	116	55.78 $\pm$ 17.44	15.48 $\pm$ 2.59	28.86 $\pm$ 1.04	4.36 $\pm$ 3.93	55

Note. N = sample size; edu = years of education; MMSE = mini-mental status exam; CES-D = center for epidemiological study depression scale. The groups did not differ significantly on any of the demographic variables.