Review: '**The BDNF val66met polymorphism affects activity-dependent secretion of BDNF & human memory & hippocampal function'** (Egan et al, 2003)

Gareth Stack

2,488 Words

Introduction

Influenced by a growing body of animal research indicating a role for BDNF in early and late hippocampal long term potentiation, synaptic plasticity, and spatial and episodic memory (e.g.: Poo, 2001, cited in Egan et al, 2003), Egan et al 2003, hypothesised a common single nucleotide polymorphism, val66met, affecting expression of the proBDNF precursor, would lead to altered intercellular transport, firing dependent secretion, hippocampal function, memory, and increased risk of schizophrenia (due to the relationship between hippocampal dysfunction and schizophrenia - e.g.: Barkatakia, et al, 2005) in humans.

Egan et al 2003, carried out a multifaceted examination of the cognitive, neurochemical, and functional consequences of the BDNF val66met SNP, across a variety of in vivo, in vetro, human and animal, and sophisticated systems level experimental paradigms – from BOLD fMRI to confocal microscopy, immuno-enzyme essay, viral transfection, and virtual hippocampal legions using the n-back protocol.

This review will explore the importance of Egan et al 2003 to neuroscience on a range of axis - as a study of a dimension of cognition related to gene polymorphism in normal range human subjects; as an insight into the mechanisms of secretion and transport of BDNF; as an investigation of neurotrophin modulated variations in synaptic plasticity and normal memory range; as a multi-modal investigation of the cognitive, neurochemical and physiological effects of the isoforms of a protein; and finally as a indicator of the role of BDNF in the aetiology and treatment of neuropsychiatric disorders, addiction, and age related cognitive deficits.

Val66met Polymorphism as a dimension of cognition

Egan et al, 2003, demonstrated reduced cognitive performance on the Wechler Memory Scale (WMS-R), a test of episodic memory, related to BDNF genotype, with individuals carrying the val/met allele performing significantly worse than val/val individuals, and met/met carriers performing significantly worse than both other groups. This finding makes Egan, et al, 2003, the first paper to evidence the association between a genetic variation (a single nucleotide polymorphism - dbSNP rs6265) and a dimension of memory (mediated by hippocampal function), through the study of functional neural activity in endophenotypes associated with specific behavioural phenotypes (Inoue & Lupski, 2003) – evidencing the feasibility of studying genetically mediated variations in memory performance.

Bonne et al 2004, in their efforts to develop a model explaining maladaptive stress responses and behaviours (specifically in PTSD) through a multifaceted examination of brain structure and molecular biology, relate the functional polymorphism found by Egan et al, - resulting in diffuse perinuclear BDNF and reduced regulated secretion - to a deleterious effect on hippocampal structure and cognitive function; evidencing the importance of the relationship between cognition and polymorphism identified by Egan et al.

Egan et al 2003, is one of several papers evidencing a link between synaptic transmission and cognitive ability. Given the slower than expected identification of quantitative trait loci's for complex traits such as intelligence (Plomin et al, 2005), the evidence Egan et al provide of a dimension of cognition related to gene polymorphism in normal subjects, whilst not demonstrating a quantitative trait locus for Spearman's G, does provide one starting point for the functional genomic analysis of the genetic roots of intelligence (Plomin et al, 2005). This is supported by the demonstration of significantly diminished functioning in aspects of performance IQ in Chinese female val/met carriers (Tsaia et al, 2004).

Egan et al 2003, lend weight to the concept of intelligence as modular or domain specific – whether perceived as a collection of adaptive, heuristic, evolved psychological mechanisms (Pinker, 2002)(Buss, 1999), or as a cognitive multi

component computational model (Baddeley & Hitch, 1974) - by evidencing a *domain specific* performance differential not affecting overall intelligence, associated with a common single nucleotide polymorphism, in a cognitive variable highly correlated with general intelligence (Conway et al, 2003).

Secretion and Transport of BDNF

Egan et al 2003, demonstrated deficits in the punctate and distal distribution and regulated secretion of BDNF in in vitro rodent met66 hippocampal neurons; providing an insight into the mechanisms which underlie the extracellular secretion and intracellular transport of BDNF. Kuei et al 2003, suggest that Egan et al's, identification of a disassociation between constitutive secretion of BDNF (unaffected by the val66met polymorphism), and of regulated secretion (by contrast heavily mediated by the met nucleotide substitution), indicate the importance of the pro-region of BDNF in both the labelling of mature BDNF for transport to synapses, and the regulation of firing dependent secretion.

Val66met polymorphism has no functional effect on the mature BDNF protein, thus differences in the production and release of BDNF between the three variations of val66met (valval, valmet, and metmet), provide information as to the functions of the proBDNF precursor in the cleavage and distribution of mature BDNF (Hariri, 2003). The mechanism by which the met allele inhibits regulated release of BDNF may be via the disruption of transport of BDNF from trans Golgi bodies into secretory granules (Thomas & Davies, 2005), suggesting that val66 proBDNF may function to facilitate such trafficking (Lu, 2003).
The inhibition in episodic memory performance found by Egan et al, 2003, may be a result of such changes in proBDNF regulated, firing dependent, BDNF secretion and intracellular transport within the hippocampus, or by contrast, developmental problems in hippocampal neural circuit integrity, resulting from a developmental deficits in BDNF cleavage or release (Hariri, 2003).

Whichever their aetiology, the changes val66met SNP enact on cognitive performance seem to be related to structural defects in the hippocampal formation. Deficits in brain volume have been identified as related to val66met SNP, Buller et al, 2006, demonstrated an 11% reduction in hippocampal volume related to possession of the val/met allele; Similarly Szeszko et al, 2005, evidenced via MRI both a main effect of val66met genotype on hippocampal volume, and a greater relative decrease on brain volume in schizophrenic patients, related to the met allele.

BDNF related variations in episodic and declarative memory and synaptic plasticity

BDNF's relevance in human memory and hippocampal function had not been examined directly prior to the study under discussion (Egan et al, 2003). Egan et al, demonstrated that variations in normal episodic memory range involve BDNF, the hippocampal level of which is determined at a genetic level - significantly establishing a genetically determined element of variance in human memory performance; and replicating in humans the underlying mechanisms of LTP and spatial memory found in lower animals (BDNF signalling, see Mizuno et al, 2003) – suggesting an evolutionary conservation of function underlying human episodic memory.

In a follow up to Egan et al 2003, Hariri et al, 2003, carried out tests of hippocampus dependent declarative memory as related to val66met polymorphism in normal subjects. Hariri et al, 2003, found a significant effect of val66met polymorphism in the identification of stimuli as novel vs. previously presented - indicating an effect on declarative memory of endophenotype, such that the interaction of genotype and hippocampal activity accounted for 25% of recall variance in a stepwise regression analysis. This research, inspired by the association between the val66met polymorphism and cognitive function identified by Egan et al, evidences a role in declarative memory for BDNF, and more generally adds weight to the perception of BDNF as a facilitator of regulated synaptic plasticity and LTP.
Similarly, animal studies such as Berchtold et al 2005, (which hypothesised a correlation between the priming of molecular memory of BDNF release and priming of learning and memory), and Adlard et al 2005 (which measured exercise induced BDNF production as related to age), have built on Egan et al's, 2003 study to evidence the importance of BDNF for variations in normal episodic memory range, and hence the importance of identifying the variables regulating release of this neurotrophic. Val66met SNP related variations in episodic memory and cognitive function have more recently been confirmed in an aging human population (Miyajima et al, 2005).

Lu, 2003, suggests that ProBDNF may preferentially activate neurotrophic receptor p75NR, while mature BDNF may bind more often to trkB neurotrophic receptors;

triggering specific cascades upon receptor activation, at both pre and post synaptic sites; thus the dichotomous forms of BDNF may have opposite effects on synaptic transmission and plasticity.
Supporting this assertion, Koponen et al 2004, demonstrated in transgenic mice over expressing the BDNF receptor trkB.TK+, relatively decreased hippocampal LTP, but improved memory, facilitated learning and reduced anxiety. Similarly, gene knockout models deficient in the trkB receptor (with conditional mutations to prevent premature death), have demonstrated deficits in learning, plasticity and CNS structure (Xu et al, 2000, cited in Koponen et al, 2004). Together these studies provide a strong confirmation of the importance of the role of BDNF in human memory and synaptic plasticity identified by Egan et al.

The demonstration by Egan et al, that activity dependent release of BDNF is required for the formation of some types of learning and memory in adults (Davies, 2005), may provide one example of the classical mechanism of learning described by Hebb's, 1949 postulate. BDNF can be defined as a modulator of Hebb synapse's in some forms (spatial, episodic, verbal) of memory formation – an aspect of the growth process or metabolic change underlying learning. BDNF is thus of primary importance to the hippocampal dependent conversion of short term associations held in 'reverberatory circuits' to long term memories, in the expression of both early and late long term potentiation (LTP); itself described by Kuei & Federoff, 2003, as 'an electrophysiological representation of synaptic plasticity'.

Multiple Methodologies & Functional Imaging

Gabrieli & Preston, 2003, describe Egan et al's integration of genetics, cellular and molecular biology, and functional brain imaging - in investigation of memory function differences in response to genetic variation -, as 'a remarkable example of integrative research', due to its successful combination of experimentation at all available levels of observation. Although the impact of the val66met genotype represented only a small degree of variance on task performance ($F = 3.89$, $df = 2, 591$, $p = .02$; over the sample of both normal and schizophrenic patients and siblings), this both lends credence to the polygenetic nature of cognitive functions, and evidences the resolution of the methodologies used (Gabreili & Preston, 2003).

Egan et al 2003, represents an example of the imaging of genetic effects on neurocognitive functioning; evidencing the importance of brain imaging beyond its use in determining the functional neuroanatomy of cognitive processes (Posner, 2004). Such a paradigm allows the measurement of small effect sizes in manageable samples; without recourse to the substantial sample sizes previously required, or danger of the confounding factors (e.g.: individual non-genetic variability) previously engendered by the subjective neuropsychological testing of populations genotypically heterozygous for a given allele (Mattay & Goldberg, 2004).

Egan et al 2003, make use of both the temporal resolution provided by functional magnetic resonance imaging (to record hippocampal activation), and the spatial resolution of proton magnetic resonance spectroscopic imaging (to measure neuronal integrity and synaptic abundance) in normal range patients. Research such as the study under review is pioneering the use of functional brain imagining determining the impact of specific genes and environmental stimuli on the circuits responsible for modulating behaviour in humans.

Mood Disorders, Neuropsychiatric Illnesses, Aging and Addiction

Egan et al, 2003, found a significant reduction in hippocampal N-Acetyl Aspartate, a purported indicator of neuronal density, related to val66met genotype; indicating lower neuronal density in individuals possessing the met allele.
The reduced episodic memory and hippocampal NAA – found in subjects possessing the BDNFmet SNP, may (with the acknowledgement that doubts have been raised as to the use of NAA as a neuronal marker – i.e.: Barker, 2001) indicate a role of BDNF in the maintenance of intracellular pathways (e.g.: phosphoinositol cycle, Wnt and PI-3K-Akt pathways) which have been found to ameliorate a variety of psychiatric illnesses and mood disorders (Coyle & Duman, 2003)(Hashimoto, et al, 2004).

The val66met substitution has been associated with a variety of psychiatric disorders including Alzheimers Disease, Parkinsons Disease, Bipolar Disorder, Depression and OCD (Chen et al, 2004), and has been linked to increased depression and anxiety scores on the State-Trait Anxiety Inventory (Lang et al, 2005); thus the efficacy of mood stabilizers, antidepressants and ECT, which act to promote neurogenisis and plasticity, may be mediated by BDNF.

One model of action of antidepressants, posited by Castren 2003, suggests a 'positive feedback loop' of BDNF linked CREB activation, leading to the facilitation of (socially determined) functionally useful synapses in stem cells activated into neurogenesis by antidepressants. A recent study, indicating a role for BDNF in the mediation of aversive social learning, lends credence to this hypothesis. Berton et al, 2006, found that mice repeatedly confronted with stressful encounters with larger dominant animals, became trained to exhibit social avoidance – but that this learning failed to take place when BDNF was knocked out from the mesolimbic dopamine pathway, via a viral vector.

Ultimately the role evidenced by Egan et al 2003, for BDNF in hippocampal function, and its possible contribution to the diathesis of neuropsychiatric disorders, may lead to the development of novel psychopharmacological interventions for mood disorders (Hashimoto, et al, 2004).

More recent studies have failed to find a significant role of genetic variants in BDNF (specifically the rs6265 val66met SNP) in schizophrenia or major depressive disorder (e.g.: Schumacher, et al, 2005). However Gomez-Pinilla & Vaynman, 2005, suggest a prenatal role for BDNF in the aetiology of schizophrenia, based on the disruption of BDNF directed functional synaptic development in compromised prenatal environments.

Investigations of age related cognitive deficits have attempted to localize cognitively significant genetotypic differences; while such differences are most often quantiatively differentiated and polygenetically inherited, some aspects of age related degeneration have been investigated for qualitative traits (Deary et al, 2004). The identification by Egan et al 2003, of individual differences in memory related to a SNP, provides a potential point of investigation in determining the heritability and interactions of genes and haplotypes relating to cognitive aging (Deary et al, 2004).

Interestingly an investigation of the val66met substitution in a cohort of substance abusers (Cheng et al, 2005) found a significant association between homozygous possession of the *val/val* allele and substance abuse; suggesting an association between higher CNS BDNF levels and vulnerability to addiction – potentially due (based on Egan et al 2003's findings of a met allele related reduction in regulated BDNF release) to relatively increased euphoria in val/val individuals following drug use. Cheng et al's, research provides evidence for the intriguing possibility that possession of the met SNP may have an adaptive protective function.

Conclusion

While Egan et al's study failed to demonstrate an association between BDNF val66met genotype and schizophrenia, the paper did, as its title suggests, establish a role for BDNF in mediating functional variations in human memory, synaptic plasticity and hippocampal activation. More than that, Egan et al's pioneering study established the viability of an integrative systems level approach to the study of genetic variations on human cognition, provided new insights into the role of the proBDNF precursor and the transport and secretion of BDNF, and paved the way for a new understanding of neurodenerative disorders and aging.

Adlard, P.A., Perreau, V.M., Cotman, C.W. (2005) The exercise-induced expression of BDNF within the hippocampus varies across life-span. Neurobiology of Aging, 26, 511-520.

Baddeley, A.D., Hitch, G.J. (1974). Working Memory, In G.A. Bower (Ed.), Recent advances in learning and motivation (Vol. 8, pp. 47-90), New York: Academic Press.

Barker, P.B. (2001) N-Acetyl Aspartate—A Neuronal Marker? Annals of Neurology, 49, 4.

Barkatakia, I., Kumarib, V., Dasa, M., Taylora, P., Sharma, T. (2005) Volumetric structural brain abnormalities in men with schizophrenia or antisocial personality disorder. Behavioral Brain Research, article in press.

Berchtold, N. C., et al (2005) Exercise primes a molecular memory for brain-dervied neurotrophic factor protein induction in the rat hippocampus. Neuroscience, 863-861.

Berton, O., McClung, C.A., DiLeone, R.J., Krishnan, V., Renthal, W., Russo, S.J., Graham, D., Tsankova, N.M Bolanos, C.A., Rios, M., Monteggia, L.M., Self, D.W., Nestler, E,J (2006) Essential Role of BDNF in the Mesolimbic Dopamine Pathway in Social Defeat Stress. Nature, 311, 5762, 864-868.

Bonne, O., Grillon, G., Vythilingam, M., Neumeister, A., Charney, D.S. (2004) Adaptive and maladaptive psychobiological responses to severe psychological stress: implications for the discovery of novel pharmacotherapy. Neuroscience and Biobehavioral Reviews, 28, 65-94.

Bueller, J.A et al (2006) BDNF Val66Met Allele Is Associated with Reduced Hippocampal Volume in Healthy Subjects. Biological Psychiatry, article in press.

Buss, D.M. (1999) Evolutionary psychology: The new science of mind. Nova York: Allyn & Bacon.

Castren, E. (2003) Neurotrophic effects of antidepressant drugs. Current Opinion in Pharmacology, 4:58-64.

Cheng, C. et al (2005) Brain-derived neurotrophic factor (Val66Met) genetic polymorphism is associated with substance abuse in males. Molecular Brain Research, 140, 86, 90

Chen, Z., Patel, P.D, Sant, G., Meng Chui, Teng, K.K, Hempstead, B.L, Lee, F.S. (2004) Variant Brain-Derived Neurotrophic Factor (BDNF) (Met66) Alters the Intracellular Trafficking and Activity-Dependent Secretion of Wild-Type BDNF in Neurosecretory Cells and Cortical Neurons. The Journal of Neuroscience, 24, 4401-4411.

Conway, A. R. A., Kane, M. J., & Engle, R. W. (2003). Working memory capacity and its relation to general intelligence. Trends in Cognitive Sciences, 7, 547-552.

Coyle, J.T., Duman, R.S. (2003) Finding the Intracellular Signaling Pathways Affected by Mood Disorder Treatments. Neuron, 157-160.

Deary, I.J, Wright, A.F, Harris, S.E, Whalley, L.J, Starr, J.M (2004) Searching for genetic influences on normal cognitive ageing. Trends in Cognitive Sciences, 8, 4, 2004.

Egan, M.F, Kojima, M., Callicott, J.H. Goldberg, T.E, Kolachana, B.S, Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M, Lu. B, Weinberger, D.R (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell, 112, 257-269.

Gabrieli, J.D.E., Preston, A.R, (2003) Visualizing Genetic Influences on Human Brain Functions. Cell, 144.

Gomez-Pinilla, F., Vaynman, S. (2005) A "deficient environment" in prenatal life may compromise systems important for cognitive function by affecting BDNF in the hippocampus. Experimental Neurology, 192, 235-243

Hariri, A.R., Goldberg, T.E., Mattay, V.S., Kolachana, B.S., Callicott, J.H., Egan M.F., Weinberger, D.R. (2003) Brain-Derived Neurotrophic Factor val 66 met Polymorphism Affects Human Memory-Related Hippocampal Activity and Predicts Memory Performance. The Journal of Neuroscience, 23, 6690-6694.

Hashimoto, K., Shimizu, E., Iyo, M. (2004) Critical role of brain-derived neurotrophic factor in mood disorders, Brain research. Brain research reviews. 45(2):104-14

Hebb, D.O. (1949) The organization of behavior: a neuropsychological theory. New York: Wiley.

Inoue, K., Lupski, J. R. (2003) Genetics and genomics of behavioral and psychiatric disorders. Current Opinion in Genetics & Development, 303, 309.

Koponen, E., Voikar, V., Riekki, R., Saarelainen, T., Rauramaa, T., Rauvala, H., Taira, T., Castren, E. (2004) Transgenic mice overexpressing the full-length neurotrophin receptor trkB exhibit increased activation of the trkBPLC; pathway, reduced anxiety, and facilitated learning. Molecular and cellular neurosciences. 26(1):166-81

Kuei, C.L, Seung, T.L, Federoff, H.J. (2003) Review: Neurotrophin secretory pathways and synaptic plasticity. Neurobiology of Aging, 1135-1145.

Lang, U.E., Hellweg, R., Kalus, P., Bajbouj, M., Lenzen, K.P., Sander,T., Kunz, D., Gallinat, J. (2005) Association of a functional BDNF polymorphism and anxiety-related personality traits. Psychopharmacology, 180, 1, 95-99.

Lu, B. (2003) Pro-Region of Neurotrophins: Role in Synaptic Modulation. Neuron, 39, 735-738.

Pinker, S. (2002) The Blank Slate : The Denial of Human Nature and Modern Intellectual Life. London: Penguin.

Plomin, R. Kennedy, J.K.J., Craig, I.W. (2005) The Quest for Quantitative Trait Loci Associated with Intelligence. Intelligence, in press.

Posner. M.I. (2003) Imaging a Science of Mind. Trends in Cognitive Sciences, 7, 10.

Mattay, V.S., Goldberg, T.E (2004) Imaging genetic influences in human brain function. Current Opinion in Neurobiology. 14:239-247.

Miyajima, F., Payton, A., Pendleton, N., Horan, M., Ollier, W., Deakin, W., John, S. (2005) Positive association of brain-derived neurotrophic factor (BDNF) polymorphism with cognition and memory recall in a healthy elderly population. American Journal of Medical Genetics Part B-Neuropsychiatric Genetics.

Mizuno, M., Yamada, K., Takei, N., Tran, M.H., He, J. Nakajima, A., Nawa, H., Nabeshima, T. (2003) Phosphatidylinositol 3-kinase: a molecule mediating BDNF-dependent spatial memory formation. Molecular Psychiatry, 8(2):217-24

Schumacher, J., Abou Jamra, R.A., Becker, T., Ohlraun, S., Klopp, N., Binder, E.B., Schulze, T.G., Deschner, M., Schmäl, C. Höfels, S., Zobel, A. Illig, T. Propping, P., Holsboer, F., Rietschel, M., Nöthen, M.M, Cichon, S. (2005) Evidence for a Relationship Between Genetic Variants at the Brain-Derived Neurotrophic Factor (BDNF) Locus and Major Depression. Biological Psychiatry, 59, 307, 314.

Szeszko, P.R., Lipsky, R., Mentschel, C., Robinson, D., Gunduz-Bruce, H., Sevy, S., Ashtari, M., Napolitano, B., Bilder, R.M, Kane, J.M, Goldman, D., Malhotra, A.K. (2005) Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. Molecular Psychiatry. 10 (7): 631-636

Thomas, K. Davies, A. (2005) Neurotrophins: A Ticket to Ride for BDNF. Current Biology, 15, 7.

Tsaia, S., Honga, C., Yuc, Y.W., Chend, T.(2004) Association Study of a Brain-Derived Neurotrophic Factor (BDNF) Val66Met Polymorphism and Personality Trait and Intelligence in Healthy Young Females. Neuropsychobiology, 49:13-16.