Supposition without appreciation for evolutionary mechanisms represents a danger to the field of evolutionary psychology. Microevolution (e.g., natural selection and genetic drift) operates in synergistic fashion with macroevolution (e.g., evolutionary history and adaptive constraints), as coordinated by developmental biology responding to an environment. In general, natural, sexual, frequency-dependent, individual, kin, group, and species selection operate on phenotypes and drive change in gene frequency across successive generations. Mutation, the founder effect, the bottleneck effect, drift, and Mendel’s fair coin represent opportunities for variation. Random variation creating synonymous base substitutions, pseudogenes, and neutral amino acids may have no evolutionary effect. Evolution can be very fast when selection is directed and strong in a large population with great diversity, but rapid modifications usually incur costs that destabilize changes. The price of change may induce maladaptation, or even dysfunction in response to environmental extremes, and this is evident in the evolution of the human brain.

Evolution fashioned a balance between the energetics (Aiello & Wheeler, 1995; Clutton-Brock & Harvey, 1980; Foley, Lee, Widdowson, Knight, & Jonxis, 1991; Herculano-Houzel, 2011; Snodgrass, Leonard, & Robertson, 2009) of high cell number for information storage and retrieval (e.g., elephants), complexity for sense data processing and calculation (e.g., sonar-dependent bats), or both as in cetaceans and primates (Herculano-Houzel & Kaas, 2011; Snodgrass et al., 2009). The crucial element in human brain evolution is plasticity, which is not merely cell growth and neurite organization but also malleable interconnectivity and targeted cell removal. Warm social contact and environmental enrichment early in life tend to support neuron development and connection retention (Diamond, 1991; Harlow & Harlow, 1965; Smith, Greenberg, Seltzer, & Hong, 2008); negative stress tends to destabilize growth and enhance apoptosis (Belsky & de Haan, 2011; De Bellis & Kuchibhatla, 2006; Hallmayer et al., 2011; Harlow, 1974; Malone, 2011c, 2011d; Slavich, Way, Eisenberger, & Taylor, 2011). These factors demonstrate gender bias and thus provide triangulation in the search for a genetic mechanism that unites developmental disorder with evolution (Malone, 2012).

The CYP19A1 gene codes for cytochrome P450 aromatase (P450arom) and is located on the long leg of chromosome 15, at 21.2 (S. A. Chen et al., 1988; Simpson et al., 1994; Zhang et al., 2004). P450arom is the enzyme that converts testosterone into the most pervasive and biologically active steroid, neuroprotective estradiol (E2). The region on CYP19A1 that codes for P450arom must splice onto one of nine primate species yields a linear regression, \( R^2 = .994 \), adjusted \( R^2 = .989 \), \( F(3, 5) = 143.758, p < .001 \).

**Keywords**

autistogenesis, CYP19A1, plasticity, evolution, disorder
nine transcripts (Sebastian & Bulun, 2001) for specific tissue expression (Figure 1). For example, the major placental transcript contributes to increased circulating E2 in pregnant women by 2 to 3 orders of magnitude (Abramovich & Rowe, 1973). However, uniting large transcripts prior to translation permits many opportunities for transcript-level regulation and dysfunction, especially at the common splice site.

Circulating serum estradiol demonstrates wide ranging effects throughout the body and directly regulates the inflammatory response in all tissues (Bastarache et al., 2012; Bechlioulis et al., 2012; Chakrabarti & Davidge, 2013; Douin-Echinard et al., 2011; Sophonsritsuk et al., 2013; Zierau, Zenclussen, & Jensen, 2012) and is linked to autoimmunity in males (Becker, 2012). The inflammatory cascade is a system of feed-forward and feedback loops, and metabolites of these processes directly regulate gene expression in cells that reside within entirely different tissues, such as the gastrointestinal (GI) tract (Ahlquist et al., 1982; Grossman, Brazier, & Lechago, 1981; Strober & Fuss, 2011; Whittle, 1981). This is a bidirectional phenomenon and many proinflammatory compounds used by the GI as chemical messengers trigger schizophrenic individuals and exacerbate challenges with autism spectrum disorders (ASDs) and multiple sclerosis (S. M. Collins, Surette, & Bercik, 2012; Coury et al., 2012; Frye, Melnyk, & MacFabe, 2013; Maenner et al., 2012; Severance et al., 2012).

Sex hormone production peaks in the third trimester and then diminishes before birth, followed by a massive prepubertal surge (Figure 2) weeks later (Fitch & Denenberg, 1998; Forest, Sizoenko, Cathiard, & Bertrand, 1974; Main, Schmidt, & Skakkebaek, 2000). Potentially neurotoxic levels of testosterone are converted by P450arom into E2 which stimulates neurogenesis, neurite outgrowth, elongation, synaptogenesis, and regeneration, and mitigates apoptosis, necrosis, and physiological debridement (Arai, Sekine, & Murakami, 1996; Beyer, 1999; Fukudome et al., 2003; Garcia-Segura, 2008; Hao et al., 2006; Ma et al., 1993; Prange-Kiel & Rude, 2006; Quesada, Lee, & Micevych, 2009; Rasmussen, Torres-Aleman, MacLusky, Naftolin, & Robbins, 1990; Zhang et al., 2004), including connections to olivary cells otherwise deficient in autistics with male bias (Malone, 2011a, 2012). Studies indicate E2 regulates neurogenesis and apoptosis throughout the cortex (Arai et al., 1996; Fukudome et al., 2003; Raimundo et al., 2012; Real, Meo-Evoli, Espada, & Tauler, 2011) differentially by region and is context-specific through α- and β-estrogen receptor subtypes on cortical cells, during different periods of development (Kritzer, 2006; Ma et al., 1993; Rasmussen et al., 1990).

Converting normal levels of testosterone into E2 enhances verbal and spatial performance (Cherrier et al., 2007; Spritzer et al., 2011), promotes the development of Purkinje cell axons within the ventromedial nucleus (VMN) of the hypothalamus with male bias (Keller, Panteri, & Biamonte, 2010), and regulates cell size, number, and activity in the fusiform gyrus (Bölte et al., 2006; Hall, Szechtman, & Nahmias, 2003; van Kooten et al., 2008). E2 enhances long-term potentiation (Mukai et al., 2007; Woolley, 2007), object recognition and spatial memory (Luine, Jacome, & MacLusky, 2003) with male bias, modulates working memory (Sinopoli, Floresco, & Galea, 2006), and promotes antioxidant metabolism that inhibits neuroinflammatory processes with female bias (Sen, Khanna, & Roy, 2006). It is interesting to note that a recent study (Sharawy, Hassan, Rashed, Shawky, & Rateb, 2012) also demonstrates that E2 levels differentially regulate the hypothalamic-pituitary-adrenal (HPA) axis response under stress.

E2 also regulates docosahexaenoic acid (DHA) synthesis, which is significantly produced in females only (BUDGE, 2003). The highly complex CYP19A1 gene contains nine major tissue specific transcripts separate from the aromatase coding. RNA for tissue and the enzyme must link prior to translation, thus the common splice site represents a region for regulation and failure. CYP19A1 is unusually large, with increased probability for mutation, maladaptive methylation, histone modification, dysregulation from compromised feedback messengers, and the influence of more than a dozen major alleles identified thus far. The transcript region for Bone (~ 20kb), Breast Cancer / Adipose and Ovary (~0.5), and Breast Cancer & Endometriosis (~0.2) are combined due to their comparatively small size and adjoining positions in the sequence. The illustration is thus not to scale and is adapted from The Systems Theory of Autistogenesis: Putting the Pieces Together (p. 5), by J. P. Malone, 2012, Los Angeles, CA, Sage Publications. Copyright 2012. Adapted with permission.
Jones, & Wootton, 2002; Giltay, Gooren, Toorians, Katan, & Zock, 2004), to provision the unborn and nursing infant while protecting maternal prosociality. Placental uptake is highest during the final trimester which also represents the greatest phase of neurogenesis, neurite formation, and arborization (Green & Yavin, 1998). E2 also regulates glutamatergic neurotransmission and so provides protection against excitotoxicity (Blaylock & Strunecka, 2009; Choudhury, Lahiri, & Rajamma, 2012; Spampinato, Merlo, Nicoletti, & Sortino, 2012) and glutathione-mediated redox/antioxidant capacity (Rose et al., 2012). DHA is essential for neuron growth, elongation, arborization, neurite outgrowth, synaptic pruning, and provides protection against apoptosis and necrosis (P. Green & Yavin, 1998; Hashimoto et al., 2005; Horrocks & Yeo, 1999; Ikemoto, Kobayashi, Watanabe, & Okuyama, 1997; Kan, Melamed, Offen, & Green, 2007; Kawakita, Hashimoto, & Shido, 2006; Okada et al., 1996).

DHA, in a physiologically correct ratio (Hashimoto et al., 2002; Hashimoto et al., 2005; Rapoport, Ramadan, & Basselin, 2011; Rapoport, Rao, & Igarashi, 2007) with arachidonic acid (AA), enhances synaptic transmission and long-term potentiation (Itokazu, Ikegaya, Nishikawa, & Matsuki, 2000; Poling, Vicini, Rogawski, & Salem, 1996; Vreugdenhil et al., 1996; Young, Gean, Chiou, & Shen, 2000; Young, Gean, Wu, Lin, & Shen, 1998). DHA reduces apoptosis by promoting phosphatidylserine (PS) production, up-regulating antiapoptotic genes, and inhibiting proapoptotic metabolites (Horrocks & Farooqui, 2004; Kim, Akbar, &
Kim, 2001; Kim, Akbar, Lau, & Edsall, 2000; Lukiw et al., 2005; McNamara, 2010; Morris et al., 2003). Dysregulation of the omega-3/omega-6 fatty acid balance within the brain promotes increased neuroinflammatory degeneration (Rao, Kim, et al., 2011; Rao, Rapoport, & Kim, 2011). This proinflammatory reaction, including oxidative stress, results in apoptosis, cell debris, and poorly functioning yet intact cells removed by brain macrophages and microglia (Malone, 2011b, 2011c; Paolicelli et al., 2011), and so this broad sequence of events is both directly and indirectly regulated by CYP19A1 expression (Malone, 2012).

McCarthy (2008) indicated differing aspects of the developing brain are immune to E2’s fast and potent influence at various stages, thought to prevent aberrant neuronal development (Malone, 2012). This explains why estradiol may lose efficacy or even enhance risk of neurodegenerative processes following stroke in women older than 65 (Azcoitia, Arevalo, De Nicola, & Garcia-Segura, 2011). However, in preterm infants fed high-dose DHA (1% total fatty acids) infant milk formula demonstrated improved Bayley Mental Development (MDI) scores at 18 months corrected age in females only (Makrides et al., 2009). Because oxytocin receptor (OXTR) sites are also regulated by E2 (Nissenson, Floret, & Hechter, 1978), social and emotional attachments (Ainsworth, 1969; Ainsworth, Blehar, Waters, & Wall, 1978; Bard, 2012; Bard & Gardner, 1996; Bowlby, 1969, 1988; Bretherton, 1992; Harlow & Harlow, 1965; Maestripieri, 2003; Russell & Ainsworth, 1981; van Ijzendoorn, Bard, Bakermans-Kranenburg, & Ivan, 2008) are strongly influenced by E2 (F. S. Chen & Johnson, 2012; Krueger et al., 2012), as are the dynamics of male aggression (Love et al., 2012; Trainor, Lin, Finy, Rowland, & Nelson, 2007). Therefore, CYP19A1 expression broadly influences the sensitive periods of gender-specific emotional and social behavior, and the brain plasticity supporting primate cognition responsive to a dynamic environment (Malone, 2011d, 2012).

Since Dunbar (1992), many have suggested the process of hominid brain evolution accelerated by selection favoring a neurology that facilitates behaviors such as (a) imitation, (b) social mediation, (c) Machiavellian strategizing, and (d) the interpersonal relationships of coalition formation (Byrne & Corp, 2004; Call & Tomasello, 1998; Schillaci, 2008; Wilson, Kahlenberg, Wells, & Wrangham, 2011; Wrangham, 1993). Numerous studies have explored the issue of brain development through evolution but disappoint, in part by failing to account for the differences in study samples due to developmental stage (for a review, see Healy & Rowe, 2007). The critical aspect to human brain evolution is phenotypic plasticity; primate brains experience tremendous cell proliferation postpartum, selective synaptic pruning in response to an infinitely variable environment, “hard-wiring” due to myelination (Figure 2), and CYP19A1 is principal to each of these processes.

The aim of the current study is twofold. The first purpose was to explore the evolution of CYP19A1 as evidence indicates developmental derailment is not an exclusively human condition (Bastian, Sponberg, Suomi, & Higley, 2003; Brent, Lee, & Eichberg, 1989; Brüne, Brüne-Cohrs, McGrew, & Preuschoft, 2006; Capitanio, Mendoza, Mason, & Maninger, 2005; Clay, 2012; Conti et al., 2012; Davenport, 1979; Davenport & Menzel, 1963; Davenport & Rogers, 1970; Davenport, Rogers, & Rumbaugh, 1973; Ferrodiasian et al., 2011; Goodall, 1986; Harlow & Harlow, 1965; Hook et al., 2002; Kalcher-Somersguter, Preuschoft, Craulsheim, & Franz, 2011; Kempes, Gulickx, van Daalen, Louwerse, & Sterck, 2008; Malone, 2011d; Nash, Fritz, Alford, & Brent, 1999; Ridley & Baker, 1982). The cognitive flexibility that allows for invention and manipulation of tools, whether material or social, rests at the core of primate brain evolution hypotheses (Barton, 1996; Byrne & Corp, 2004; Call & Tomasello, 1998; Dunbar, 1992, 1998, 2010; Dunbar & Shultz, 2007; Joh & Dunbar, 1997; Joly, 1966; Kudo & Dunbar, 2001; McGrew, 1992; Pawlowski, Lowen, & Dunbar, 1998). Because the human brain does not mature unilaterally duringontology, nor has it done so through phylogeny, there may be genetic mechanisms that link selection to developmental neurobiology.

While it is true that brain size and complexity correlate to physiological and ecological factors (Allman, McLaughlin, & Hakeem, 1993; Armstrong, 1985; Clutton-Brock & Harvey, 1980; Dunbar & Shultz, 2007; Harvey & Krebs, 1990; Walker, Burger, Wagner, & Von Rueden, 2006), the author suggests that genetic mechanisms supporting the social brain hypothesis would correlate less as taxonomy goes phylogenetically afield. Such a mechanism must also account for the gender-biased differences in developmental pathology (Malone, 2011d, 2012) and the evidence that neocortical volume positively correlates to group size in females but not to males (Lindenfors, 2005). Therefore, this study first seeks to determine if the CYP19A1 gene (a) demonstrates a strong phylogenetic trend and (b) if its orthologous relationship correlates to previously hypothesized mechanisms for human brain evolution.

Organisms possess genotypes that permit deviations in developmental pathways in response to varying environmental conditions (Scoville & Pfiender, 2010). The most crucial aspect of the primate brain is neither size nor “executive brain” volume (Reader & Laland, 2002, p. 4436). Because learning is directly tied to synaptic malleability (Blumenfeld-Katzir, Pasternak, Dagan, & Assaf, 2011), selection has focused on regulation of brain remodeling through development. The systems theory of autistogenesis suggests human brain evolution resulted in maximal phenotypic plasticity, to accommodate multiformal selective pressures without concurrent change in genetic conformation, yet liable to epigenetic and transcript-level expression regulation (Malone, 2011d, 2012).

A rapidly growing consensus indicates a system linking the neurodevelopmentally sensitive response to environmental stimuli with the genetics of neuroinflammation combines...
to predispose ASD pathogenesis with male bias (Angelidou et al., 2012; Becker, 2012; Hu, 2013a, 2013b; James, 2008, p. 15; Malone, 2012; Rossignol & Frye, 2011), and alterations to one or more components within the system may initiate neurodegenerative feedback. Though both genes and environment seem necessary, neither appears independently sufficient for ASD pathogenesis in the preponderance of cases (James, 2008; Malone, 2012), a metabolic endophenotype linking genes with environment is theorized (Angelidou et al., 2012; Becker, 2012; Hu, 2013a, 2013b; James, 2008; Malone, 2011c). This suggests that a predisposing genetic profile could exist within an individual without developmental disorder who did not receive environmental insult during developmentally sensitive periods (Angelidou et al., 2012; Hu, 2013a, 2013b; James, 2008; Malone, 2012). Likewise, this view suggests that an individual without a genetic burden could develop disorder under very great environmental stress during the same early life stage (Angelidou et al., 2012; Hu, 2013a, 2013b; James, 2008; Malone, 2012).

Malone (2011c) first hypothesized that CYP19A1 plays a principal role in brain plasticity and developmental disorder due to more than a dozen known alleles, opportunities for single-nucleotide polymorphism influence, possible epigenetic imprinting, miRNA regulation, and other forms of transcript-level expression modification that may alter developmental trajectories. Therefore, if CYP19A1 complexity trends with phylogeny and correlates strongly to previously hypothesized drivers of human brain evolution, the second aim of this study is to answer whether the gene can provide genetic accommodation specific to (a) brain region, (b) by gender, (c) across developmental stages, and (d) with broad expression variability.

**Method**

To calculate orthologies (Kent et al., 2002), a multiz alignment (Blanchette et al., 2004) of CYP19A1 from the February 2009 (GRCh37/hg19) human assembly of the Genscan, Ensembl, RefSeq, and UCSC gene database was produced using: chimpanzee (P. troglodytes, October 2010; CGSC 2.1.3/panTro3); western lowland gorilla (G. gorilla gorilla, May 2011; Sanger Institute gorGor3.1/gorGor3); Sumatran orangutan (P. pygmaeus abelii, July 2007; WUGSC 2.0.2/ponAbe2); northern white-cheeked gibbon (N. leucogenys, January 2010; GGSC Nleu1.0/nomLeu1); rhesus macaque (M. mulatta, January 2006; MGSC Merged 1.0/rheMac2); common marmoset (C. jacchus, March 2009; WUGSC 3.2/calejac3); dolphin (T. truncates, February 2008; Broad Institute turTru1); microbat (little brown bat; M. lucifugus, July 2010; Broad Institute Myoluc2.0/myoluc2); megabat (large flying fox, P. vamprus, July 2008; Broad Institute pteVam1); African elephant (L. africana, July 2009; Broad/loxArf3), American opossum (M. domestica, October 2006; Broad/monDom5); platypus (O. anatinus, March 2007; WUGSC 5.0/ornAna1); chicken (G. gallus, May 2006; WUGSC 2.1/galGal3); anole lizard (A. carolinensis, May 2010; Broad AnoCar2.0/anoCar2); African clawed frog (X. tropicalis, November 2009 (JGI 4.2/xenTro3); stickleback fish (G. aculeatus, February 2006; Broad/gasAcu1); lamprey eel (P. marinus, March 2007; WUGSC 3.0/petMar1).

The above species provide a skeletal framework for the subphylum Vertebrata, thus representing a foundation for an evolutionary perspective, with special emphasis on nonhuman primates. A simple alignment of Neanderthal CYP19A1 is determined to assess this unique gene in another species of Homo as a limited form of test for internal validation. A Neanderthal CYP19A1 composite is produced from 6 ANFO-mapped fossil samples (Feld1, Mez1, Sid1253, Vi33.16, Vi33.25, Vi33.26) aligned against the human genome (Briggs et al., 2009; R. E. Green et al., 2010) using the UCSC Genome Browser (Blanchette et al., 2004; Karolchik et al., 2003; Kent, 2002; Kent et al., 2002; Stenzel, 2009). Because modern Homo sapiens share a more recent common ancestor with Neanderthal than any nonhuman pri- mate, CYP19A1 should demonstrate organization nearly identical to the current human model, particularly if the gene demonstrates an evolutionary trend through the extant primate lineage.

Dunbar’s (1992) original model (Figure 3) presented neocortex ratio (NCR) as an independent variable and group size as the dependent variable, stating that “the interest lies in the consequences of brain size” (p. 9). This perspective neglects environmental circumstances that may induce last- ing group size change regardless of brain development. Because, unlike Dunbar, this study is concerned with the cause of human brain evolution, NCR becomes the
dependent variable and group size is one of the independent variables for the purpose of the model. This study considers that while growing through neurologically sensitive stages within an ever-dynamic social milieu (Rodseth, Wrangham, Harrigan, & Smuts, 1991; Sutcliffe, Dunbar, Binder, & Arrow, 2012), situated within an environment of limited resources, selection (Wilson et al., 2011; Wrangham, 1993) operated on individual variability to propel primate brain evolution. Therefore, due to its contribution to plasticity, environmentally triggered patterns of neuronal remodeling, and modulation of gender typical social behavior, CYP19A1 is a factor.

What has become known as “Dunbar’s equation” is corrected with current information regarding orangutan (Rodman, 1993; Singleton & van Schaik, 2002; te Boekhorst, Schürmann, & Sugardjito, 1990; Utami, Goossens, Bruford, de Ruiter, & van Hooff, 2002) and gorilla (Yamagiwa, Kahekwa, & Basabose, 2003) range and social group dispersion. Dunbar (1992) log-transformed all data due to curvilinear relationship between group size and NCR, and performed the regression on reduced major axes as this provides greatest estimate of relation when errors are unknown, though this creates an added false visual sense of linearity (Figure 3). These species previously described by Dunbar as existing in a group size of 1 are here considered as living in a social group of 2+ as courtship and mating is assumed to be a complex social interaction (Schillaci, 2008) within local if not overlapping environments.

The ratio of neocortex volume to whole brain volume is the dependent variable as it accounts for executive function, though it is easy to imagine a small primate evolving a NCR greater than human, yet still in possession of a brain no larger than a walnut. To fashion a more complete model, brain mass (Deaner, Isler, Burkart, & van Schaik, 2007; Dunbar & Shultz, 2007) is included so that neuronal density that varies within and between brain regions (C. E. Collins, Airey, Young, Leitch, & Kaas, 2010) and the scaling factor (Clark, Mitra, & Wang, 2001, Herculano-Houzel, 2009; Herculano-Houzel & Kaas, 2011) become a feature of the model. The female body cavity delimits the general size of the fetus, and the size of the female pelvis restricts the size of the neonatal brain, so brain volume enables some accounting for general body size and encephalization quotient in primates (Deacon, 1997; Jerison, 1973).

Following species-specific data correction, SPSS v 18 was used to perform a regression with NCR as the dependent variable. Square root transformed group size and brain mass data (TGR and TBM, respectively) with CYP19A1 genetic orthology are independent variables. Unlike Dunbar (1992), the axes remain intact to prevent added visual impression of linearity. Because visual interpretation of graphic analysis suggested a phylogenetic trend through vertebrate phylogeny, with particular development in primates, a CDS FASTA alignment (Karolchik et al., 2003) output was produced from nine primate species to derive the amino acid sequence alignment against the February 2009 (GRCh37/hg19) human CYP19A1 assembly. Amino acid sequence was chosen over nucleic acid because each transcriptome sequenced represents an imaginary construct representing each species with no easy accounting for substitutions to synonymous codons. The BLAST-like alignment tool (BLAT; Kent, 2002) is used to determine orthology.

If it is established that CYP19A1 complexity does trend with phylogeny and that it correlates strongly to previously hypothesized drivers of human brain evolution, then the UCSC Genome Browser (Kent, 2002) is used to align the Ensembl, Genscan, RefSeq, and UCSC Gene human genome databases against data from exon microarray expression in the fetal brain (Johnson et al., 2009), histone mapping through brain development by gender (Cheung et al., 2010), TargetScan miRNA regulatory sites (Friedman, Farh, Burge, & Bartel, 2009; Grimson et al., 2007; Lewis, Burge, & Bartel, 2005), RNA transcription levels (ENCODE Project Consortium et al., 2011), brain DNA methylation (Maunakea et al., 2010; Morin et al., 2008; Robertson et al., 2007), and the presence of simple nucleotide polymorphisms (SNPs; Sherry et al., 2001). Assessment of CYP19A1 expression and regulation from the above data provides evidence relative to genetic accommodation specific to (a) brain region, (b) by gender, (c) across developmental stages, and (d) with broad genetic variability.

### Results

Phylogenetically, CYP19A1 does not fully organize until placental vertebrates (Figure 4) and appears to play a reasonably comparable role whether bat, elephant, or dolphin, until the rise of Platyrrhini (New World monkeys) and Catarrhini (Old World monkeys and apes). Visual examination of the multiz alignment suggests that CYP19A1 begins to approximate human conformation in primates, especially as all tissue-specific exons (Sebastian & Bulun, 2001) appear to align with gaps and start/stop sequences, but visual representation is deceptive as the130k nucleotide sequence is graphically compressed. Individual CYP19A1 orthology for the nine primate species to current human data was determined (Table 1). Furthermore, the Neanderthal CYP19A1 composite produced by aligning the Feld1 Mez1 Sid1253 Vi33.16 Vi33.25 Vi33.26 sequences (Briggs et al., 2009; R. E. Green et al., 2010) against the human genome through the UCSC Genome Browser (Blanchette et al., 2004; Karolchik et al., 2003; Kent, 2002; Kent et al., 2002; Stenzel, 2009) demonstrates similarity to the current human model.

The square root procedure is considered the most conservative transformation to use for curvilinear relationships (Mertler & Vannatta, 2010) and was applied to group size (TGR) and brain mass (TBM) but was not necessary for NCR or CYP19A1 orthology. The Mahalanobis distance procedure was used and the $\chi^2$ critical value = 18.467, $df$ = 4 indicates no outliers. A regression was produced using NCR as the dependent variable. The independent variables include TGR, TBM, and CYP19A1 orthology as an estimate for
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Figure 4. Alignment of CYP19A1 with 21 vertebrate species to the human genome. The dashed lines indicate regions identified as transcripts that allow for tissue specific expression: 1. Placenta major, 2. Placenta minor 2, 3. Skin & Adipose tissues, 4. Fetal tissues, 5. Brain, 6. Placenta minor 1, 7. Ovary and Breast Cancer, Endometriosis, and Bone, 8. Aromatase enzyme. CYP19A1 organization does not follow a trend in elephant, microbat (the vision dependent megabat is provided for contrast), dolphin, or the prosimians, but expands and unifies in monkeys and finally appears on the same chromosome in apes. Upward signals from the selective sweep scan indicate those sections with greater Neanderthal specificity, while downward signals are suggestive of positive selection in early humans (Green et al., 2010).

Table 1. CYP19A1 Orthology for Nine Key Primate Species With the Current Human Genome Sequence.

| Common name          | Species                | % orthologous | NCR  | Group no. |
|----------------------|------------------------|---------------|------|-----------|
| Chimpanzee           | P. troglodytes         | .9981         | 3.22 | 53.5      |
| Western lowland gorilla | G. gorilla gorilla   | .9962         | 2.65 | 17.0      |
| Sumatran orangutan  | P. pygmaeus abelii    | .9886         | 2.47 | 5.0       |
| Hamadryas baboon    | P. hamadryas           | .9791         | 2.76 | 51.2      |
| Rhesus macaque monkey | M. mulatta             | .9733         | 2.60 | 39.6      |
| Common marmoset     | C. jacchus             | .9339         | 1.52 | 8.5       |
| Philippine tarsier  | T. syrichta            | .8582         | 1.09 | 2.0       |
| Gray mouse lemur     | M. murinus             | .8668         | 1.23 | 9.5       |
| Northern greater galago | O. garnettii         | .8820         | 0.94 | 2.0       |

Most methods yield the same slope estimates when $R^2 > .9$ (Mertler & Vannatta, 2010) and the linear regression was produced, $R^2 = .994$, adjusted $R^2 = .989$, $F(3, 5) = 143.758$, $p < .001$, two-tailed (Figure 5) using SPSS v 18. This model accounts for 99% of variance in primate brain evolution evolutionary trend toward increased phenotypic plasticity.
without threat of multicollinearity as the variance inflation factor for all variables is below 10 and all collinearity tolerance statistics are above 0.1 (Mertler & Vannatta, 2010; O’Brien, 2007). A reaction surface (Wu et al., 2007; Yap, Yao, Das, Li, & Wu, 2011) of TGR, TBM, and NCR on CYP19A1 is produced using MS Excel® (Figure 6) that illustrates significant changes from prosimians, to monkey, and finally to great apes.

It is clear that CYP19A1 has increased in size and complexity in a way that trends with phylogeny and strongly correlates to previous models describing human brain evolution. Data from exon microarray expression (Johnson et al., 2009) demonstrate that within the fetal brain, regions otherwise considered key for tissue-specific transcription become fundamental aspects of fine regulation in at least 13 regions of the brain and for both hemispheres (Figure 7). Histone mapping provides evidence of regulation through developmental stages by gender, and the data sets (Figure 8) appear to validate previous hypotheses (Cheung et al., 2010; Malone, 2012). Seven-nucleotide seed targets (CYP19A1: miR-539, ATTTCTCA, score: 65 and CYP19A1: let-7/98, CTACCTCA, score: 98) were detected (Figure 8) within all known miRNA families conserved across mammals from multiz alignments (Friedman et al., 2009; Lewis et al., 2005) and assigned scores based on context (Grimson et al., 2007).

RNA transcription levels (ENCODE Project Consortium et al., 2011) from seven cell lines (lymphoblastoid, embryonic stem cell, human skeletal muscle myoblasts, human umbilical vein endothelial cells, human erythromyeloblastoid leukemia cells, normal human epidermal keratinocytes, and normal human lung fibroblasts) suggest greater degrees of regulation than previously specified (Figure 8) by Sebastian and Bulun (2001). Regulation of alternative promoters by tissue-specific DNA methylation (Figure 8) was determined and MRE-seq, MeDIP-seq, H3K4me3 ChIP-seq, RNA-seq and RNA-seq (SMART) libraries were sequenced (Maunakea et al., 2010; Morin et al., 2008; Robertson et al., 2007) using data available through National Center for Biotechnology Information (Accession Number SRP002318).

Single nucleotide polymorphisms, small insertions, and deletions with at least 0.01 minor allele frequencies were determined in an attempt to isolate common variants in the general population (Sherry et al., 2001) relative to UCSC and Genscan gene databases. Taken together, the above data sets appear to validate another study (C. E. Collins et al., 2010), and provides strong evidence that CYP19A1 demonstrates the capacity for genetic accommodation (a) specific to individual brain regions, (b) by gender, (c) across all developmental stages, and with (d) broad variability previously hypothesized (Malone, 2012).

**Discussion**

Evolutionary biology must inform evolutionary psychology if it is to contribute to the study of development and its disorder. For some species, genetic accommodation is the phenotype upon which selection critically operates. The evolution of myriad regulatory mechanisms on primate brain development permits wide ranging synaptic reorganization in response to as many ecotypes. Thus, epigenetic tuning of infant genotype expression, and a plastic response to stimuli during stages of developmental sensitivity, may result in a broad spectrum of phenotypes from the same genotype. The richness or paucity of environmental stimuli defines an ecotype’s character; stimulus type, duration, and intensity describe its potential for influence; yet the individual’s phe-
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phenotypic plasticity, as modified by gender and age of exposure, will modify the consequences.

Unfortunately, great phenotypic plasticity is expensive because it requires multiple overlapping systems operating in concert. The only gene capable of so broadly influencing the human brain’s malleable periods of cognitive, emotional, and social sensitivity with gender bias in health and disorder is CYP19A1. This work presents a new framework to approach many forms of developmental disorder and offers new hope to those suffering many pervasive forms. Furthermore, by assessing tissue- and site-specific expression regulation through techniques such as histone mapping, identification of allelic differences, miRNA characterization, and accurate accounting of meaningful polymorphisms (see Anthoni et al., 2012) true biological assay and molecular routes to treatment appear well within reach. Detailing each site-specific regulatory phase for CYP19A1 may reveal a large pool of data to illuminate the genesis of developmental, mood, and personality disorders in every stage of life.

Histones may be thought of as molecular spools around which tightly wound DNA is wrapped to pack the almost 2-m strand into a single cell. When an aspect of the genome is actively used, it must unwind from the histone, and so histone mapping seeks to label regions where genetic expression is active and potentially modified in some way. Transcription levels may be altered by normal cell mechanisms, and by chemicals from elsewhere in the body, such as certain nutrients or toxins. Depending upon the importance of these modifications, the brain may be altered to adapt to new environmental challenges.

Figure 7. Exon expression by brain region. Consolidated, and then expanded for visualization, the exon microarray expression data from 13 brain regions of late mid-fetal human brains are grouped by regional mean as log-ratios. CYP19A1 regulation occurs throughout fetal and neonatal development, influences learning through its impact on brain plasticity, and is linked to developmental disorders due to its direct and indirect regulation of neuroprotective mechanisms and the neuroinflammatory response.
and complexity of the gene, a wide range of phenotypic profiles arise from histone transcription regulation, and it is satisfying to find that histone mapping of CYP19A1 appears to validate several previous studies (Kritzer, 2006; Luine et al., 2003; Ma et al., 1993; McCarthy, 2008; Rasmussen et al., 1990). Because many of the techniques described in this work can be performed with formaldehyde-preserved tissues, it is now feasible to track the evolution of site-specific regulatory mechanisms with fine detail across all brain regions and throughout the entire chordate phylum.

The miRNA data presented (Figure 8) suggest that primary expression regulation of P450arom gene in placenta occurs at the level of transcription and the tissue-specific region is conserved throughout the mammalian class (Helgen, 2011). It is perhaps important to note that the same tissue-specific transcript carries the weight of Neanderthal-specific deviation (Figure 4). It is reasonable to suggest Neanderthal experienced no difference in expression, due to synonymous substitutions and equivalent amino acid variations, but this could represent maternal reproductive adaption in response to dietary DHA availability. Human CYP19A1 transcription levels are highest in regions dedicated to reproductive tissues and the brain (Figure 8), and these areas show positive selection in early humans (Figure 4).

Increased gyral white matter in the human prefrontal cortex (PFC) suggests selection in primates for risk assessment, emotional restraint, attention maintenance, meta-awareness, working memory, imitative learning, goal-directed behavior, communication (including use of gaze), and decision making (Barth, Reaux, & Povinelli, 2005; Beran & Evans, 2006; Boesch, 1993, 1996; Casey, Galvan, & Hare, 2005; Casey, Tottenham, Liston, & Durston, 2005; Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Courchesne et al., 2000; Evans & Beran, 2007a, 2007b; Giedd et al., 1999; Jurado & Rosselli, 2007; Lenroot & Giedd, 2006; Miller, 2000; Miller & Cohen, 2001; Müller, Radtke & Wissing, 2002; Suddendorf & Whiten, 2001; Voytek & Knight, 2010; Xi et al., 2011). Though ascribing a “reason” for some trait to evolve is often problematic, these data seem to correlate with

![Figure 8. Fine regulation of CYP19A1 by gender, across lifetime developmental stages, as detected by histone mapping, miRNA regulation, transcription level, cytosine-guanine (CG) methylation, and known simple nucleotide polymorphisms (SNPs). This degree of regulation is necessary because CYP19A1 transforms testosterone into neuroprotective estradiol and coordinates the conversion of omega-3 fatty acids into DHA while competitively inhibiting proinflammatory AA. Axonal elongation, myelination, neurite outgrowth, arborization, synaptogenesis, generation of neuroprotectin D1, inhibition of apoptosis, and targeted physiological debridement are thus modulated by CYP19A1 with extreme regulation.](image-url)
Table 2. Preliminary Results Using the Orthology Correlation Technique on 158 Genes.

| Demonstrates positive correlation | Little to no positive correlation |
|-----------------------------------|---------------------------------|
| ADH5, ADORA1, ADORA1, ADORA2A,   | ACHE, APBB1, ASCL1, BMP4, BMP4, |
| AF361886, ALK, APBB1, APOE, APP,  | CACNA1G*, CDH9*, CDH10*,        |
| ARTN, BCL2, BDNF, BDNF, BMP2,     | NNTAP2*, EN2*, FADS2, FOXP2*,   |
| BMP8B, CDK5RAP2, CHRM2, CREB1,    | GABRA4*, GABRB3*, GSTP1*,       |
| CTH, CXCLI, CYP19A1, DCX, DISC1,  | HOXA1*, HOXB1*, MAFG, MAFK,     |
| DISC2, DLG4, DLL1, DNAJC3, DRD2,  | MAPK3*, MDK, MDK, MECP2*, MET*, |
| DRD2, DVL3, E2F1, E2F8, EFNB1,    | NDN, NEUROG1, NLGN3*, NRXN1*,  |
| EGF, EIF2AK3, EIF2S1, EP300, ERBB2,| OLG2, OXTR*, POU4F1, POU4F1,    |
| ESR1, FADD, FADS1, FADS3, FAD56,  | PRKCB1*, PRL*, PRLR*, RELN*,    |
| FGF2, FLNA, GDNF, GLO2, GLRX,     | ROBO1, SERT*, SHANK3*,          |
| GLRX3, GPR3, HAGH, HDAC4,         | SLC25A12*, SLC6A4*, SOX2, SOX8,|
| HDAC4, HES1, HEY1, HEY2, HEYL, IL3,| TPH1, TPH2, TRPV2, TRPV4, UBE3A*|
| KEAP1, LONRF1, LONRF2, LONRF3,    |                                 |
| MAP2, MEF2C, MET, MLL, NDN, NDP,  |                                 |
| NEUROD1, NEUROG2, NF1, NFE2L2,   |                                 |
| NF-kB, NOG, NOTCH1, NOTCH2,       |                                 |
| NR2E3, NRCAM, NRG1, NRPI, NRPI,   |                                 |
| NTF3, NTNI, ODZ1, OLIG2,          |                                 |
| PAFAH1B1, PARD3, PAX3, PAX5,      |                                 |
| PAX6 PSMB5, PTN, RAC1, RTN4,      |                                 |
| S100A6, S100B, S14017, S1H2L,     |                                 |
| SLIT2, SOD1, STAT3, TFB1M, TFB2M,|                                 |
| TGFB1, TH, TNR, TRPV1, TRPV3,     |                                 |
| TRPV6, VEGFA                       |                                 |

Note: More than two dozen genes listed above were previously considered linked to developmental disorders, including autism, and are labeled with an asterisk (*). It is important to understand that pathology purely due to genetics is considered a disease and not a disorder, and while each of those listed may induce a disease with behavioral characters strikingly similar to those diagnostic of autism spectrum disorders, they seldom explain any aspect of the gender bias, the influence of environmental stimuli, and never both together.

(a) increased DHA production in mammary tissues (Caspi et al., 2007; Lammi-Keefe, Rozowski, Parodi, Sobrevia, & Foncea, 2008), (b) increased DHA uptake by the placenta (Campbell, Gordon, & Dutta-Roy, 1996; Dutta-Roy, 2000), (c) both of which are required for proportionally thicker cortical white matter in the growing human brain (Allman et al., 1993; Allman, Hakeem, & Watson, 2002; Smaers, Schleicher, Zilles, & Vinicius, 2010).

For many decades, the common approach to genetics was to study artificially induced and naturally occurring mutations as a means to understand normal gene expression. This author asserts that as great phenotypic plasticity is the primary character trait selected for, the search for genes linked to developmental disorder that also demonstrate phylogenetic trends in orthology will reveal those genes most critical to human brain evolution. This author is currently assessing genes known linked to human brain development and disorder to determine what may be the core genomic set responsible for human brain evolution (preliminary results provided in Table 2). Those genes demonstrating higher orthology further from primates specifically, and toward placental mammal, marsupial, monotreme, reptile, and so on provide estimation for when in evolution those genes became most selectively advantageous. It is important to point out that the FOXP2 and HOX genes did not display strong positive orthologous correlation, suggesting that while these genes were important to the evolution of a central nervous system, they did not play a central role in human brain evolution specifically.

Authors’ Note

Raw data for the exon microarray expression may be obtained through the NCBI Gene Expression Omnibus http://www.ncbi.nlm.nih.gov/geo. All in silico hybridizations, histone mapping, DNA methylation assessment, and assessment of CYP19A1 SNPs were processed using the UCSC Genome Browser on Human February 2009 (GRCh37/hg19) Assembly, the UCSC, Ensembl, Genscan, and RefSeq databases, and ENCODE data.

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**Author Biography**

J. Patrick Malone explores the rise of developmental disorder from an evolutionary perspective. Through neurogenetics, neurophysiology, and comparative developmental psychopathology, he seeks to answer whether human brain evolution required selection for predisposition to disorder.