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Research paper

Patterns of anterior versus posterior white matter fractional anistotropy concordance in adult nonhuman primates: Effects of early life stress

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ABSTRACT

Introduction: Functional neuroimaging studies report global prefrontal dysconnectivity in mood disorders, supporting the notion of widespread disruptions in brain networks. Microscopic alterations in white matter (WM) tracts – which possess neuroplastic properties and play a central role in brain connectivity – are interrogated herein in the context of brain dysconnectivity. Early life stress (ELS), an antecedent to human mood disorders, induces WM alterations in volumetrics and integrity. We hypothesized that nonhuman primate infants exposed to ELS would exhibit persistent impairments in both frontal and posterior concordance of WM integrity, therefore contributing to global brain dysconnectivity.

Methods: Using a 3T MRI, diffusion tensor imaging (DTI) was performed on 21 adult male Bonnet macaques, 12 of whom had been raised under variable foraging demand (VFD) conditions and nine of whom had been raised under normative conditions (Non-VFD). As representative of anterior regions, fractional anisotropy (FA) concordance between anterior corpus callosum (ACorpusC) and anterior limb of the internal capsule (ALIC) was examined. For posterior regions, FA concordance between posterior corpus callosum (PCorpusC) and posterior limb of the internal capsule (PLICA) and between PCorpusC and occipital WM was examined. Examination of posterior FA was explored in the context of frontal markers of neuroplasticity.

Results: A concordant relationship for FA between left ALIC and ACorpusC was evident in Non-VFD-reared subjects, but significantly absent in VFD-reared subjects. For left posterior regions, FA concordance between PLICA and PCorpusC and occipital WM and PCorpusC was evident in VFD-reared and not Non-VFD-reared subjects. The posterior concordance in VFD was significantly distinguishable from the deficit in anterior concordance FA in VFD.

Conclusions: The findings support the view that disrupted emotional integrity of the maternal-infant attachment process affects normative synchronous development of frontal white matter tracts but creates errant posterior concordance and also disrupts an inverse relationship between posterior white matter tracts and markers of neuroplasticity. We provide preliminary evidence that a concordant relationship between capsular–callosal FA may become discordant, providing a putative mechanism for prefrontal functional brain dysconnectivity.

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1. Background

Childhood abuse and neglect is a major antecedent for a variety of human adult disorders including mood (De Bellis and Putnam, 1994; Van der Kolk, 2003; Gonzalez et al., 2012; Danese et al., 2009) and anxiety disorders (Van der Kolk, 2003; Ackerman et al.,

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1998), metabolic syndrome (Hepgul et al., 2012), chronic pain disorders (Danese et al., 2009; Danese et al., 2008; Hosang et al., 2013) and cardiovascular disease (Gonzalez et al., 2012; Saariaho et al., 2011; Walsh et al., 2007). Preclinical models of early life stress (ELS) have mostly utilized rodents (Plotsky et al., 2005) and nonhuman primates (Barr et al., 2004; Coplan et al., 1996) primarily manipulating the integrity of maternal care (Liu et al., 1997). We have utilized an animal model of ELS in bonnet macaques exposed to maternal variable foraging demand (VFD), a paradigm in which infants are reared by mothers subjected to an experimentally-induced perception of food uncertainty without caloric deprivation (Rosenblum and Paully, 1984). VFD-reared subjects exhibit timidity (Jackowski et al., 2011) and loss of "behavioral plasticity" – a term applied to adaptive modifications of behavior (Molteni et al., 2004) – in response to a human intruder in comparison to healthy controls (Rosenblum et al., 2001). Moreover, VFD-reared macaques exhibit persistent elevations in CSF concentrations of the stress neuropeptide, corticotropin releasing-factor (CRF) (Coplan et al., 2005), and a myriad of other neurotransmitter (Coplan et al., 2014a), metabolic (Perera et al., 2011), neuroanatomical, including corpus callosum cross-sectional area deficits (Jackowski et al., 2011; Coplan et al., 2014b), molecular (Coplan et al., 2010; Mathew et al., 2003) and neuroplastic alterations (Perera et al., 2011). This extensive array of alterations each appear capable of contributing to the affective distress observed in VFD-reared subjects (Rosenblum and Paully, 1984) and replicate abnormalities observed in human anxiety and mood disorders (Coplan et al., 1995). However, whether these discrete alterations in VFD-reared subjects interact as an aberrant neural circuitry has not been previously addressed.

More recently, psychiatric disorders in general, and mood disorders in particular, have been hypothesized to stem from disrupted neural computations across networks of regions (Palaniyappan and Cousins, 2010). Recent functional neuroimaging studies have reported global prefrontal dysconnectivity in bipolar I disorder (Anticevic et al., 2013), major depressive disorder (MDD) (Wang et al., 2014), obsessive compulsive disorder (OCD) (Anticevic et al., 2014) and schizophrenia (Yang et al., 2014), supporting the notion of widespread disruptions in brain networks in severe psychiatric disorders (Anticevic et al., 2013). Abnormal neuroplasticity and cellular resilience (Perera et al., 2007) have been invoked to produce impairments in these distributed neural networks (Carlson et al., 2006). A study in major depressive disorder indicated that methylation of the BDNF promoter region was associated with reduced regional white matter integrity (Choi et al., 2015), suggesting that white matter may also be vulnerable to neurotrophic compromise. One hypothesis – based on studies in patients with generalized anxiety disorder – is that posterior regions, such as the occipital lobe, may be relatively hyperactive or hypertrophied whereas anterolateral regions, such as the hippocampus and prefrontal cortex, are hypoactive and hypotrophic (Abdallah et al., 2012). Treatment studies using riluzole – an antiglutamatergic agent – show anteroposterior divergent structural and molecular effects in GAD and bipolar depression patients (Abdallah et al., 2012, 2013; Brennan et al., 2010; Mathew et al., 2005). Anteriorly, treatment response is associated with a parallel increase in gray matter volume and concentrations of N-acetylaspartate (NAA), a marker of neuronal integrity (Abdallah et al., 2013). Posteriorly, anxiolytic effects were associated with reduced occipital gray matter volume and NAA (Abdallah et al., 2012, 2013; Brennan et al., 2010). Moreover, a reduction in occipital, but increase in prefrontal, glutamate levels following treatment of patients with MDD correlated with successful anxiolytic and antidepressant response (Abdallah et al., 2014; Zhang et al., 2013). The implications of this anterior/posterior divergence in psychiatric disorders and its treatment response, interfaced with the notion of global brain dysconnectivity remains to be elucidated.

Fractional anisotropy (FA), a measure derived from diffusion tensor imaging (DTI) (Beaulieu, 2002), assesses the degree of directionality of water diffusion within the white matter tracts (Hasan et al., 2004). FA is relatively high in parallel tracts of axons, whereas FA is relatively reduced in demyelinating conditions (Salat et al., 2005). Reduced FA in the absence of gross pathology of white matter may represent a subtle form of impairment of normative structural organization of axons (Foong et al., 2002) and potentially contribute to global brain dysconnectivity. Reversal of reduced frontal WM FA in late-life depression through antidepressant intervention—electroconvulsive therapy —implies that WM tracts possess recuperative neuroplastic properties (Nobuhara et al., 2004). Preclinical studies indicate that BDNF enhances WM integrity by increasing concentrations of myelin basic protein and facilitating oligodendrocyte proliferation (McTigue et al., 2001; Wong et al., 2013). Anticevic et al. (2013) have articulated that "decreased global brain connectivity in a disease state might suggest decreased participation of a particular brain region in broader networks, whereas increased global brain connectivity might suggest a pathological broadening or synchronization of functional networks."

With respect to white matter, concordance of FA between distinct, anatomically unrelated regions invokes the presence of a common neuroplastic influence with putatively salutary functional consequences. In the current study, as representative of anterior regions, FA concordance between anterior corpus callosum (Jackowski et al., 2008, 2011) and anterior limb of the internal capsule (Coplan et al., 2010) was examined. The anterior limb of the internal capsule contains fibers running from the thalamus to the frontal lobe and fibers connecting the cortex with the corpus striatum (Coplan et al., 2010). From the anterior corpus callosum, fibers radiate from the genu to the prefrontal cortex (Moeller et al., 2005). In the case of psychopathology, a concordant relationship between capsular–callosal FA may become discordant, providing a mechanism, at least in part, for prefrontal brain dysconnectivity. We hypothesized that between-region concordance of FA could conceivably reflect neuroplastic homogeneity, facilitating orderly distribution of brain networks, whereas neuroplastic inhomogeneity would facilitate dysconnectivity and negative affective states. We have already shown that mean FA of the anterior limbs of the internal capsule correlates inversely with right and left amygdala volume, a marker of early life stress, specifically in VFD versus Non-VFD (Coplan et al., 2014b). In addition, elevations of CSF 5-HIAA, a putative indicator of reduced serotonin neurotransmission, inversely predicted mean FA of the anterior limbs of the internal capsule but only in VFD-reared versus normally-reared subjects (Coplan et al., 2014a).

As representative of posterior regions, FA concordance between posterior corpus callosum (Jackowski et al., 2008, 2011) and posterior limb of the internal capsule (Bengtsson et al., 2005) and between posterior corpus callosum and occipital white matter (Coplan et al., 2010) was examined. The posterior body of the corpus, known as the splenium (Putnam et al., 2010), communicates somatosensory information between the two halves of the parietal lobe and the visual cortex at the occipital lobe. The posterior limbs of the internal capsule carry the corticospinal tracts (Bengtsson et al., 2005) whereas the occipital white matter projects to the visual cortex (Agartz et al., 2001). We hypothesized that FA concordance in posterior regions would be relatively more evident in VFD-reared versus control subjects, confirming an anterior/posterior divergence. As an auxiliary hypothesis, we postulated that FA of posterior ROIs would correlate positively with indicators of reduced neurotrophic status and inversely with stress markers. We would therefore provide additional evidence of an anterior/posterior WM FA divergence as relates to non-WM structures.