Adolescent anxiety and aggression can be differentially predicted by electrocortical phase reset variables

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ABSTRACT

Increasing evidence supports the notion that both internalizing (e.g., anxiety) and externalizing (e.g., aggression) behavioral dysregulation are associated with abnormal communication between brain regions. Electroencephalographic (EEG) signals across two electrode sites are said to be coherent with one another when they show consistent phase relations. However, periods of desynchrony with shifting of phase relations are a necessary aspect of information processing. The components of EEG phase reset ('locking' when two regions remain in synchrony, and 'shifting' when the two regions desynchronize momentarily) show dramatic changes across development. We collected resting EEG data from typically developing 12 to 15-year-olds and calculated phase shift and lock values in the alpha frequency band across 14 pairs of electrodes varying in inter-electrode distance. A composite measure of participants' aggression levels was positively associated with phase shifting, particularly in the low alpha frequency range, most strongly over the left hemisphere, consistent with the relatively greater left-prefrontal activity reported in aggressive adults. A composite measure of anxiety levels was positively associated with alpha phase locking at sites over both hemispheres, consistent with changes in connectivity reported during anxious thinking in adults. Associations with anxiety could not be explained by traditional EEG coherence measures and suggest that phase shifting and locking might provide an important non-invasive associate of clinically problematic behavior.

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1. Introduction

Adolescence is a period characterized by major biological, psychological and social changes that can affect the developing adolescent's ability to self-regulate and these changes coincide with the onset of many forms of psychopathology (Lewinsohn, Clarke, Seeley, & Rohde, 1994; Paus, Keshavan, & Giedd, 2008). Of particular interest here are increased incidence of anxiety and aggression, markers of emotional and social dysregulation respectively.

Both anxiety and aggression have been associated with specific patterns of communication between neural regions. Aberrant connectivity has been observed in some anxiety disorders (Liao et al., 2010; Marchand, 2010) and in some of those prone to aggressive behavior (Hofman & Schutter, 2009; van Honk, Harmon-Jones, Morgan, & Schutter, 2010), using fMRI and TMS connectivity techniques. The direction of these aberrations varies across studies

with Liao et al. (2010) reporting decreased connectivity in those with social anxiety disorder relative to controls within both motor and visual networks, and increased connectivity in a self-referential network involving medial prefrontal regions. The strength of the coherent activity in some of these networks is associated with symptom severity. Two other research groups (Decety, Michalska, Akitsuki, & Lahey, 2009; Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009) report that youth prone to aggressive behavior show reduced intrahemispheric connectivity (specifically between limbic and prefrontal structures important to emotion regulation).

There are, however, electroencephalographic (EEG) coherence and other connectivity measures that may better capture the moment to moment changes in functional connectivity that occur between neural regions (see e.g., Sporns, Tononi, & Edelman, 2000). Examples include the work of Hinrichs and Machleidt (1992) who used traditional alpha EEG coherence measures and observed globally *decreased* alpha coherence together with increases in peak alpha frequency during anxious thinking in an adult sample. Knyazev, Savostyanov, and Levin (2005), however, found *increased* levels of low alpha coherence (adjusted to each participant's peak

frequency, but generally 8–10 Hz) correlated positively with increased levels of state anxiety in an adult sample. Thus, the specific direction of coherence patterns associated with anxiety is unclear at present, and discordant results may be partially attributable to which frequencies within the alpha range are examined.

With respect to aggression, Hinrichs and Machleidt (1992) observed globally increased alpha coherence in participants during aggressive cognition, but their results did not address whether these relations would extend to trait measures of the same construct. Little other work has addressed the association between EEG measures of connectivity and aggressive behavior.

In sum, aberrant connectivity may be associated with anxiety and increased connectivity may be associated with aggressive states. Important for the present work, both Hinrichs and Machleidt (1992) and Knyazev et al. (2005) report on average coherence values across the whole scalp providing little to no information on the scalp locations of group and state differences despite fMRI and TMS work suggesting that these differences may be regionally specific (e.g., Hofman & Schutter, 2009; Liao et al., 2010; Marchand, 2010; van Honk et al., 2010). In the present study we test whether these reported state differences in coherence extend to stable trait measures and we aim to provide improved topographical detail on the observed effects.

2. EEG connectivity

There are a variety of ways to measure cortical communication or connectivity within EEG recordings, and each may yield different insights into the nature of the communicative differences observed in anxiety and aggression. Traditional EEG coherence measures such as the one used by Hinrichs and Machleidt (1992) estimate the strength of the linear cross-correlations between two time series (i.e., recordings from two electrodes) within a frequency band (e.g., alpha). These are linear measures which assume a constant phase value within windows of data, but EEG recordings have been shown to be highly nonlinear (Kaplan, Fingelkurts, Fingelkurts, Borisov, & Darkhovsky, 2005). Time-dependent instantaneous phase measures have been used to capture the nonlinear aspect of EEG connectivity, such as the entropy-based method of Tass et al. (1998) and the mean phase coherence of Mormann, Lehnertz, David, and Elger (2000). Windowing techniques are used to quantify periods of phase synchronization but are unable to identify specific times when the two time series become dissimilar from one another. EEG signals across two sites are said to be coherent with one another when they show synchronous phase relations, and traditional measures quantify these time periods well. However, periods of desynchrony, characterized by a shifting of phase relations, are a necessary aspect of information processing. Balance between synchronization (phase locking between two regions) and desynchronization (phase shifting) is essential for normal brain function (Garcia Dominguez et al., 2005; Hong et al., 2004; Stam, van der Made, Pijnenburg, & Scheltens, 2003), and windowed measures do not quantify this important dynamic. We suggest that separating out these distinct states of information processing may be important for understanding the cortical communicative differences observed in those with poorly regulated social and emotional functioning (e.g., anxiety and aggression).

Thatcher and colleagues have developed methods to examine phase shift and phase locking events in continuous EEG data, using what is called the phase reset cycle. A phase reset consists of a brief phase shift representing the reorganization of brain resources, and then a prolonged period of phase locking. Phase shift periods typically last from 20 to 80 ms and are followed by a longer period of phase locking which typically lasts 500 to 1000 ms, but actual times depend strongly on the frequency band of interest. Thatcher and colleagues (e.g., Thatcher, North, & Biver, 2008) describe phase

shifting as a period of uncertainty and instability and phase locking as a period of stability and low uncertainty in neural networks. During the phase shift period, relevant neural assemblies that are not in a refractory period are identified as available to bind together in a communicative network on the global and/or local level. When phase locked, these neural assemblies are able to mediate a given cognitive or psychological function. Thus, phase shifting can be conceptualized as a reorganization of resources and a preparatory period for future network integration while phase locking can be conceptualized as the period during which this network integration occurs on either the global or local level (see also Pikovsky, Rosenblum, & Kurths, 2003). Thatcher et al. (2008) suggest that there is an ideal balance of phase shifting and locking necessary for optimal cognitive performance, such that when phase shift duration is too long then there is increased noise in the network and a reduced number of neurons available for subsequent phase locking. Conversely, when phase lock duration is too long then there is less flexibility in the network (Thatcher et al., 2008). We hypothesize that dysregulation in such neural networks may manifest itself as dysregulation in psychological functioning.

Phase reset patterns are not static across development. Thatcher and his colleagues (2009) obtained measures of phase reset length across varying distances of the cortex from a large sample of children ages 3 months to 16 years. Interestingly, they report a lengthening of both phase shift and phase locking durations during the adolescent period (Thatcher, North, & Biver, 2009), consistent with the puberty-linked changes in white matter that have previously been documented in this age range (see e.g., Asato, Terwilliger, Woo, & Luna, 2010; Peper et al., 2008).

One interesting question concerns what implications these changes might have for psychological functioning in adolescence, a particularly vulnerable time for the onset of psychopathology (Lewinsohn et al., 1994; Paus et al., 2008). Our goal was to see whether a more sensitive measure of EEG connectivity (i.e., phase reset), with its ability to parse periods of phase shifting and locking at distinct site pairs, is associated with individual differences in adolescent anxiety and aggression while controlling for at least one marker of general physical development (e.g., pubertal status). Using this more sensitive connectivity measure, in addition to dividing alpha into high and low subcomponents, may shed light on the conflicting findings of Hinrichs and Machleidt (1992) relative to those of Knyazev et al. (2005).

3. Alpha, anxiety and aggression

As mentioned previously, phase reset variables are calculated within particular frequency bands. We chose to examine phase shifting and locking in the alpha frequency band because alpha power is sensitive to anxiety in adolescents (lower in those who are high on anxiety; Eismont, Aliyeva, Lutsyuk, & Pavlenko, 2008), and is increased in calm, meditative states (Cahn & Polich, 2006). Moreover, having greater left-prefrontal cortical activity (relative to right prefrontal activity, as measured by alpha asymmetry) is associated with a higher likelihood of engaging in aggressive behavior in adult men (Harmon-Jones & Sigelman, 2001).

Thus, both connectivity and alpha have been shown to be altered in those showing high levels of anxiety and aggression, leading us to ask whether phase reset variables that presumably index neural network regulation derived from the alpha frequency band would be associated with individual differences in anxiety and aggression and whether traditional coherence measures would also show such associations. If coherence is positively correlated with both levels of anxiety (e.g., Knyazev et al., 2005) and phase locking but correlated negatively with phase shifting, then we might expect that anxiety would be positively correlated with locking, and negatively correlated with shifting. However, the state