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Late Adolescence

Critical Transitions into Adulthood

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Abstract

Adolescence is a critical stage of brain development prior to the attainment of a more mature state. The neurobiological underpinnings of this transition have been difficult to characterize, contributing to the challenges in diagnosing, treating, and preventing the neuropsychiatric diseases that commonly emerge during this developmental epoch. We propose a multidisciplinary approach to address these issues, with a focus on the changing patterns of both physiologic and pathologic brain dynamics across adolescence. We put forward the intellectual merit and scientific promises of combining multiple research modalities, encouraging longitudinal studies in humans and animal models, and the potential for contributions from computational models, including artificial neural systems. We find evidence that adolescence represents a nonlinear, discrete period of perturbation during which specific brain systems for higher cognitive, emotional, and social functions are highly, and often irreversibly, modified. Identifying the neural processes underlying these developmental modifications will help facilitate their normal expression during adolescence, and ultimately prevent their disruption and the onset of neuropsychiatric disease.

Keywords: Adolescence, plasticity, neuropsychiatric disease, neural networks, nonlinear dynamics.

Introduction

> Most of us remember adolescence as a kind of double negative: no longer allowed to be children, we are not yet capable of being adults.
>
> - Julian Barnes

The transition from immaturity and dependence on caregivers to maturity and autonomy has been experienced throughout human history; elements of this key developmental phase can be identified in organisms across the evolutionary spectrum. Understanding late adolescence and the subsequent emergence of adulthood, including the neurobiological basis of this transition, is crucial to better diagnosing and treating neuropsychiatric disorders that may arise from disturbances in these brain processes. Here, we discuss a research framework for late adolescence based on development and plasticity of brain dynamics. We also describe concepts and methods currently and prospectively available to investigate this framework, and address how to potentially translate them into improved diagnostics and therapeutics for the neuropsychiatric disorders that are prevalent in this developmental period. Specifically, our discussion is focused on the following questions:

1) How to define the neurobiological transition from adolescence to adulthood?
2) Does plasticity end with adolescence?
3) What tools and models can help better investigate the dynamical processes of the adolescent brain?
4) Why and how do specific abnormalities of brain coordination predominantly arise and remit in adolescence?
5) Can information about adolescents' neural networks improve diagnosis, treatment, and prevention of adolescent brain disorders?

Section 1: Toward a neurobiological and multidimensional description of late adolescence

The end of adolescence cannot be defined by a discrete event; it gradually emerges from a complex combination of societal and biological influences. From a societal perspective, the age range considered to encompass adolescence varies with cultural and historical circumstances. Currently, in Western cultures and societies, adolescence begins at approximately 11 to 13 years of age and ends in the late teenage years (approximately 18–19 years of age). Early adolescence typically encompasses the period from the middle school years and includes most of the pubertal development that characterizes the early part of adolescence. Late adolescence refers approximately to the period following the pubertal transition. Significant psychosocial and cognitive changes occur during this time, including increases in orientation towards peers, romantic interests, and identity exploration, as well as more sophisticated cognitive abilities, such as abstract thought, future planning and goal setting, and career exploration.

Adolescence is therefore essentially recognized as a distinct developmental period in which children begin to transition into adulthood. This typically occurs by the adoption of increasingly "adult-like" behaviors such as getting married, moving away from the family, and/or bearing children. However, anthropologists note that the extent to which adolescence is acknowledged and the way each society characterizes the transition from

childhood to adulthood varies greatly by culture. In some traditional societies, public ceremonies are used to commemorate the transition from child to adult social status. In contrast, modern industrialized societies rarely publicly acknowledge adolescence, in part because there are several developmental milestones (that occur at different ages) that are considered critical to the transition from child to adult, including completion of secondary schooling, age of legal status, getting a job, getting married or becoming a parent. We suggest that neurobiology can be leveraged to articulate the definition of the end of adolescence, as key features of this transition are reflected in measurable brain processes.

Neurobiological evidence supports the hypothesis that adolescence does not exist solely as a linear chronologic connector between childhood and adulthood. Rather, we assert that adolescence is an identifiable period of perturbation with unique hormonal, neurophysiological, and experiential features that combine to provide adaptive advantages, but also vulnerabilities. Studies have examined the developmental modifications in neural circuits central to emotion regulation and reward prediction, as well as phase-synchronization of neural oscillations during the transition from adolescence to adulthood. Emotion regulation circuits involve interactions between several subregions of the prefrontal cortices (PFC) and limbic structures that dynamically change through late adolescence. In adolescent participants, there is converging evidence for heightened amygdala activity towards threat-related stimuli that correlates with levels of trait-anxiety, while modulatory feedback from the ventromedial PFC is decreased (Hare *et al.*, 2008). Resting-state fMRI data provide support for a developmental switch in this pathway (Gee *et al.*, 2013), suggesting a positive amygdala–PFC connectivity in early childhood that changes to negative functional connectivity during the transition to adolescence. These findings can be directly linked to anatomical changes observed in long-range connections that occur in late adolescence between amygdala and medial PFC (Cunningham *et al.*, 2002). Similar nonlinear changes have been observed in the reward sensitivity and prediction-error signaling during adolescence that could account for age-specific elevated risk taking. In response to monetary (Ernst *et al*., 2005; (Galvan *et al*., 2006; (Geier *et al*., 2010), decision-making (Jarcho *et al*., 2012), social (Chein *et al*., 2011), as well as prediction error reward (Cohen *et al*., 2010), and primary reward tasks (Galvan & McGlennen, 2013), adolescents exhibit greater striatal activation relative to other age groups. Longitudinal assessments, in which over 200 participants between the ages of 10–25 years were scanned twice, confirmed that the striatum shows peak activation during the adolescent period in response to reward and risk-taking (Braams *et al*., 2015).

A nonlinear trajectory of brain coordination was also observed for the development of phase-synchronization of high-frequency oscillations. Data by Uhlhaas et al. (this volume) showed that phase-synchrony in the beta- and gamma-band increases until age 14 years, followed by a reduction during late adolescence (15–17 years), before synchrony increases sharply again in 18–21 year olds. This nonlinear development of phase-synchrony was accompanied by reorganization in the anatomical topography of phase-synchrony in the beta-band.

The increasing use of functional connectivity techniques to examine the development of networks in the human brain has been useful in identifying important maturational changes that characterize adolescence. For instance, a study comparing network connectivity between children, adolescents, and adults found that connectivity of networks associated with social and emotional functions exhibited the greatest developmental effects, while connectivity of networks associated with motor control did not differ between the three groups (Kelly *et al.*, 2009). These findings confirm a long-hypothesized organizational principle of development, demonstrating that the maturation of sensory and motor systems precedes those underlying higher cognition (Chugani *et al.*, 1987). This idea reflects the self-organizing principle of dynamic systems theory, in that complex systems such as the maturing brain develop through hierarchical, non-linear processes (Johnson & Shrager, 1996).

Several resting-state studies have demonstrated that in the development of large-scale brain systems, functional connectivity shifts from a local to distributed architecture. For example, intrahemispheric connectivity within local circuits precedes the development of large-scale interhemispheric connectivity (Fransson *et al.*, 2007). Others have found that nodes within the default-mode network are sparsely connected in children and strongly functionally connected in adults (Fair *et al.*, 2008). One group collected short (5 minutes) resting-state scans from typically-developing subjects across a range of ages to predict each individual's brain maturity across development (Dosenbach *et al.*, 2010). The best predictive feature of individual brain maturity in this study was the strengthening of and segregation between the adult brain's major functional networks.

Together, these maturational patterns provide support for the notion that brain coordination within large-scale networks during late adolescence shows profound modifications that frequently involve nonlinear trajectories that can be considered as developmental perturbation, and thus may facilitate the emergence of novel principles of large-scale interactions. It should be noted that these observations do not apply to all system-level observations during adolescence. More research is required to further delineate the functional significance of these changes for the understanding of brain coordination during development.

Although the concept of developmental perturbation may help define adolescence, the patterns of these changes across different brain processes observed at multiple scales follow significantly variable trajectories. Several examples serve to illustrate this point:

i) molecular changes: dopaminergic projections and neural concentrations of dopamine increase during adolescence, and subsequently decline throughout adulthood;
ii) synaptic changes: there is a reciprocal relationship between the number of excitatory and inhibitory synapses in the prefrontal cortex, with inflection points occurring during adolescence;
iii) structural measures of neural networks: grey matter volume decreases monotonically from middle childhood to old age (Douaud *et al.*, 2014), but there is a set of brain regions comprising lateral prefrontal cortex, frontal eye field, intraparietal sulcus, superior temporal sulcus, posterior cingulate cortex, and medial temporal lobe, which peaks in volume late during adolescence and

then shows accelerated degeneration in old age compared with the rest of the brain (e.g., in accordance to the last-in, first-out notion, also termed "Ribot's law"); white matter tracts increase throughout childhood and adolescence, reaching a plateau between the fourth and sixth decades;

iv) functional measures of neural networks: the power of postsynaptic potentials and percentage of low-frequency activity as measured by electroencephalography (EEG) follow a relatively linear trend throughout adolescence; it is speculated that this monotonic decrease in total power and magnitude of evoked brain responses may reflect a lifespan transition from rate coding to temporal coding (Muller *et al.*, 2009), allowing brain processes to involve less but more coordinated activity;

v) cognitive development: "fluid" abilities that represent individual differences in the speed and coordination of elementary processing operations show their lifespan peak in late adolescence, followed by gradual decline accelerating in old age; "crystallized" abilities, which depend on acquired bodies of knowledge, peak later in age, and show a long plateau that extends into old age.

It is unlikely that any one of these processes, or numerous others that can be assayed, individually reflects maturation. Therefore, we propose that late adolescence be defined as a transitional period in relation to a combination of inflection points and ranges of linear trends across multiple structural, molecular, neural-network, and cognitive measures (Figure 1). The confluence of these measures should lead to a more versatile definition of late adolescence, facilitating translation between data points obtained from different individuals, and strengthening correlations between chronological age ranges representing adolescence and maturity across species.

Given the profound biological and experiential changes that occur during adolescence and the relative expansion of this phase during mammalian evolution, as the brains and bodies of organisms increased in complexity, it is likely that this developmental phase serves an evolutionary purpose. At no other time in life is there greater intrinsic motivation to explore the world than during adolescence (Crone & Dahl, 2012). Adolescents are in a distinct developmental stage that facilitates all of the creativity, rebellion, and progressive thinking that characterize this period. From the perspective of brain processes, adolescence may represent an experience expectant window, during which a wide range of novel experiences is actively sought out to broaden one's model of the world, and hence improve the accuracy of predictions about future experiences. It is perhaps for this reason that the increased frequency of "surprising" events, or unexpected uncertainty (Yu & Dayan, 2005), is more welcomed in adolescence than in any other time in life. As adolescents forage for new experiences, their brains may become more accurate Bayesian predictors (Friston, 2010) that are better able, in the long run, to minimize unexpected and potentially harmful responses to actions. It is perhaps this extended period of flexibility and adaptability that has allowed our species to flourish, often at the expense of less adaptable organisms.

Section 2: Does plasticity end with adolescence?

Neural plasticity processes importantly shape development across the lifespan, and we sought to explore which of these processes are at play during the transition from adolescence to adulthood. Plasticity takes multiple forms. Structural plasticity includes the formation or elimination of long- and short-range synaptic connections. Synaptic plasticity includes the alteration of receptors, channels, and other synaptic proteins to modify synaptic weights, with the knowledge that long-term synaptic plasticity can subsequently initiate local structural plasticity.

A different form of plasticity, characterized by critical periods, has been identified during early development. These critical periods involve a confluence of neural processes that create a unique epoch during which experience can fundamentally shape neural networks and their functional capabilities, sometimes irreversibly. It is unclear, but interesting to consider, whether the concept of a critical period can be extended to adolescence. It is known that specific circuits are fundamentally modified during normal adolescence, including higher association, prefrontal, and limbic regions. There is also evidence to suggest that depriving rodents of social interaction during adolescence can lead to different effects than similar deprivation at earlier or later time points during development, and that certain forms of extinction learning are temporarily attenuated during adolescence. We suggest that it could be mechanistically relevant, and potentially clinically significant, to investigate whether adolescence represents the last normative critical period.

In a like vein, it was tentatively proposed that the typical human brain does not change its overall organization after the end of adolescence. Hence, plasticity beyond adolescence is increasingly less likely to involve reorganization of neural circuitry, and more likely to be restricted to structural changes at the local level and modification of synaptic weights. However, it seems likely that more generic mechanisms related to maturation, learning, and senescence cannot be confined to specific age periods, and that some of the mechanisms known to regulate critical period plasticity also are operating during later forms of plasticity (Takesian & Hensch, 2013).

At the more local level, available experience clearly shows that structural plasticity continues to be present after adolescence. Pretest-posttest comparisons in adults have revealed grey-matter increases after several months of juggling training, intensive studying for medical exams, foreign language acquisition, spatial navigation training, playing video games, and tracing with the nondominant hand. Similar changes have been observed after two weeks of mirror reading, a few days of signature writing with the nondominant hand, and even after only two sessions of practice in a complex whole-body balancing task. In all of these cases, plasticity is specific to the trained skill, and shows a narrow transfer gradient, if any.

Age-graded differences in plastic change deserve to gain center stage and need to be delineated through age-comparative studies (Lovden *et al.*, 2010). Cognitive development from childhood to adulthood, for example, is accompanied by an increasing control of top–down control processes over bottom–up mechanisms. This shifting balance may facilitate some aspects of plastic change, and hinder others. On a related note, local plastic change needs to be studied in a global context. For instance, the primary cortices

form part of a structured, complex learning architecture. Networks that generate and monitor new behavioral routines and action sequences belong to this architecture, and contribute to individual differences in skill acquisition. Higher-order regions like prefrontal and temporal brain areas are likely to signal and keep track of the mismatch between the current range of functioning and experienced demands. We expect reductions in mismatch due to increasing task proficiency to be accompanied by decreasing activations in these areas.

Evidence at ontogenetic and microgenetic timescales supports an *overproduction–pruning model of plasticity*. The model posits an increase in the number of synapses at the beginning of the plastic episode, which is followed by experience-dependent selective stabilization of behaviorally relevant connections and the elimination of those connections that prove to be functionally irrelevant. Using two-photon microscopy and optogenetic tools, the overproduction–pruning sequence has been observed in behaving animals with unprecedented precision in recent years (Hubener & Bonhoeffer, 2014). Plastic changes in the sensory and motor cortices are marked by the rapid formation of new dendritic spines, followed by a slower process of spine elimination, returning the overall number of spines close to pre-intervention levels. The dendritic spines that have been newly formed and retained during a plastic episode show a remarkable degree of structural stability over time, and may function as the physiological substrate for skill retention and reactivation. This process appears to be specific to the practiced skill, with different skills encoded in different dedicated sets of synapses.

Macroscopically, the overproduction–pruning model leads to the hypothesis that plasticity in the human brain, regardless of the development phase, is accompanied by an initial phase of grey-matter volume expansion followed by a period of volume renormalization. To test this hypothesis in adolescents, Wenger et al. (Wenger *et al.*, 2016) recently acquired 18 structural MR image volumes over a 7-week period in 15 right-handed young adults who practiced nondominant, left-hand writing and drawing. After four weeks of practice, increases in grey matter in both left and right primary motor cortices relative to a control group were observed; another three weeks later, these differences were no longer reliable. Time-series analyses showed that grey matter in both primary motor cortices expanded during the first four weeks and then partially renormalized, particularly in the right hemisphere, in the presence of continued practice and increasing task proficiency.

Task-related functional activations in cortical areas undergoing plastic reorganization are likely to increase during the initial period of cortical expansion, and decrease in the course of renormalization, when the pruning of new connections has led to sparser coding of task-relevant perception–action links. In fact, one may speculate that the transient increase in metabolic load at the beginning of a plastic episode gives way to a more efficient, metabolically less costly task representation at its completion. These mechanisms are likely present throughout development, but may be more easily invoked at earlier developmental stages, a hypothesis that merits further investigation with longitudinal studies of plasticity to similar stimuli across development.

Reinforcement learning from prediction errors, mediated primarily by the striatum and hippocampus, is a plastic process of particular importance during adolescence. Reinforcement learning theory is couched in the notion that we learn by interacting with our environment. Specifically, reinforcement learning is learning how to maximize rewards through trial-and-error based actions, which can also include a search for cost minimization (either physical or cognitive/emotional). Learning from the environment occurs via the neural computation of a *prediction error signal,* which is derived directly from the Rescorla-Wagner Model of classical conditioning. The discovery that the prediction error signal is coded by dopamine neurons points to the central role of the dopamine system in reinforcement learning (Schultz *et al.*, 1997).

Prediction errors occur when outcomes do not match expectations. This mismatch provides new information for the organism, which learns from this new information. A positive prediction error refers to when the outcome is better than expected. For example, if an adolescent expects her weekly allowance of $50 and instead receives $60, she experiences a positive prediction error of +$10. If she instead receives $25, then she experiences a negative prediction error of -$25. One study used a learning task to violate such expectations from participants: the outcomes of the task were unpredictably better or worse than expected. When better than expected, the adolescent group (ages 13–19 years) showed an elevated positive prediction error signal in the striatum compared to children (ages 8–12) and adults (ages 25–30) (Cohen *et al.*, 2010). With training, all participants became faster and more accurate at responding to predictable stimuli, but only the adolescent group (aged 14–19) responded more quickly to stimuli associated with a higher reward value compared with small rewards. In addition, compared with children and adults, the adolescent group exhibited higher ventral striatum responses to higher, unpredicted reward. This suggests that responsiveness to dopaminergic prediction error is higher in adolescents, which might contribute to elevated reward seeking in this age group.

An alternative notion is that a greater sensitivity to prediction errors in adolescents facilitates learning. Indeed, a study that tested adolescents' and adults' ability to learn simple associations between cues and outcomes found that adolescents outperformed adults (Davidow *et al.*, 2016). This is a remarkable finding because on many other cognitive tasks, adults tend to outperform adolescents. Adolescents showed better memory for positive reinforcement events than for negative reinforcement events, whereas adults' memory did not differentiate between positive and negative events. Congruently, the adolescent subjects' brains had greater prediction error-related activation in the hippocampus compared to adults', and significant functional connectivity between hippocampus and striatum that correlated with memory for positive reinforcement events (Davidow *et al.*, 2016).

A related study found that following positive prediction errors, there was stronger connectivity between the striatum and medial frontal cortex in adolescents and young adults (ages 13–22 years) than in children (ages 8–11 years) (van den Bos *et al.*, 2012). Similar studies have also found that adolescents, compared to adults, are more responsive to unpredictable outcomes in terms of modifying behavior in response to new information (Van Duijvenvoorde *et al.*, 2012). These studies suggest that prediction error signals help adolescents learn about the environment and, importantly, to flexibly adjust their behavior in response to the

dynamic nature of life experiences. We suggest that this flexibility is possible because of the malleability of activation in striatal and frontal networks during adolescence.

Furthermore, this malleability is likely to be affected by changes in societal and cultural norms. We note that a significant portion of the lives of adolescents in many societies is increasingly spent in virtual or online environments that have developed their own unique contingency sets and social norms. For example, online dating, where potential romantic partners can first interact anonymously, carries reduced risks of damaged self-confidence, potentially allowing expression of a more daring, diverse set of behaviors. Frequent use of text messaging with multiple members of the social group, and posting of personal information to the online environment, are now prevalent, and also offer a very different framework for prediction testing among social peers. We posit that the novel opportunity to receive frequent feedback for a more extended range of behaviors with reduced risk and effort might accelerate the learning process that leads to adulthood. Similarly, existing socially-assistive robots are increasingly being evaluated for use in clinical settings for patients with disorders such as autism or dementia (Rabbitt *et al.*, 2015). We can safely speculate that interactions with robotic agents and machines could supplement, or even substitute, human social interactions at all ages. However, it is hard to anticipate the nature of new issues (and opportunities) for social interactions caused by such societal change. How this may affect or facilitate the trajectory of learned social behaviors in adolescents will undoubtedly become a significant field of study.

Earlier in this this section, we contemplated that adolescence may function as the last normative critical period of human ontogeny, characterized by a shifting balance in the expression of different forms of plasticity (long-range structural, local structural, and synaptic). We then explored reinforcement learning from prediction errors, observing that this form of learning exhibits a key nonlinearity across development, with increased responses to positive deviations from expectation during adolescence compared to life periods both preceding and following it. Hence, we hypothesize that detailed investigation of plasticity in frontal-hippocampal-striatal networks, specifically including changes in the dopaminergic modulation of reward, is likely to be a critical starting point for attempts to provide a mechanistic account of a critical period during adolescence.

Section 3: How to track the dynamics of the late adolescent brain

A major obstacle to a better understanding of the neurobiological changes occurring during the transition from adolescence to adulthood is the relative lack of large-scale, longitudinal data from multiple modalities in both human participants and animal models. Although many challenges exist to efficient gathering of such data, we propose several key considerations and potential solutions to these issues.

One benefit of research targeting this developmental phase is that the breadth of brain processes occurring in parallel allows multiple methodological tools to have potential utility. Indeed, the combination of results from various scales of measurement and methodologies is particularly critical to obtaining a complete picture

of adolescence and its trajectory into adulthood. Several of these tools have been effectively used, and hold promise for future studies:

i) molecular: postmortem brain histology of adolescent victims of sudden death allows molecular profiling of neural tissue; histochemical analyses of tissue and body fluids can determine neurotransmitter levels; a polygenic risk score for psychiatric disease can be generated based on a peripheral blood sample to address how genetic predisposition affects the molecular landscape of adolescence and its trajectory into adulthood at the individual levels;
ii) electrophysiology: EEG and MEG permit noninvasive measurements of brain oscillations, with the possibility of using transcranial magnetic/electric stimulation to modulate these oscillations; intracranial EEG/electrocorticography, though restricted to a small number of patients undergoing neurosurgical procedures, can assay electrophysiological responses at higher spatiotemporal resolution;
iii) structural neuroimaging: changes in both gray and white matter volumes, as well as white-fiber tracts density can be determined;
iv) functional and molecular neuroimaging: positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI) can investigate task- or group-specific brain activation, metabolism and the presence of specific metabolites;
v) cognitive/behavioral testing: various higher perceptual, reward-based, and cognitive tasks can delineate patterns of cognitive function;
vi) epigenetic measures: changes in methylation status of various genes can be used to explore contribution to disease risk

Importantly, the contribution of electrophysiological, structural, and functional imaging measures is amplified when combined with behavioral data, to provide a fine-grained, multifaceted picture of developmental changes in neural function and associated behavior. In light of the multidimensional nature of adolescent changes, we propose that studies involving human participants, animal models, and neural network models can all make contributions to our neurobiological understanding of adolescence.

I. Human Participant Studies

Properly designed human longitudinal studies are critical to better understand how neurodevelopment in humans relates to behavioral and psychological change over time and characterize trajectories of development spanning childhood, adolescence, and adulthood. Decisions about the spacing and frequency of measurement occasions in many longitudinal studies often depend more on the practicalities of human subject research than on theoretical considerations about appropriate temporal sampling. This may limit the interpretability of the results obtained. Tools to optimize the statistical power of longitudinal designs at detecting effects of interest, such as individual differences in change, are available (Brandmaier *et al.*, 2015). Likewise, continuous-time modeling methods yields parameters that generalize across studies that differ in the spacing of measurement occasions (Voelkle, 2015). Adolescence is also characterized by wide

population heterogeneity, such that studies should have a large number of participants in order to be appropriately powered to detect relevant effects. Obtaining behavioral, demographic, or societal data from large (>1000) populations of adolescents can be challenging. One option that has been successful is to initiate collaborations with schools or museums, providing consistent access to many adolescents. However, there must be agreement from parents and teachers to ensure a mutually beneficial interaction for the adolescents and researchers. Another emerging option is the development of dedicated apps on smartphones to test participants on behavioral measures repeatedly throughout the day (Killingsworth & Gilbert, 2010). Such an approach can rapidly generate data from thousands of subjects, and with appropriate data quality checks could represent a viable alternative to conventional large-population studies.

Given the cost and time involved in properly conducting these human longitudinal studies, a commitment to data sharing in standardized repositories is crucial. The advancements of "big-data" can be effectively employed in this field. For instance, until recently, MEG/EEG was lagging MRI in terms of collecting and curating large data repositories of normal variants and disease phenotypes. Reasons include the lack of a standard file format for raw data and the large volume occupied by high-density recordings. Fortunately, these bottlenecks are gradually, and at least partially, being overcome by the increasing availability and versatility of software readers for most native data formats. Storage capacity, especially in the cloud, has now become ubiquitous and more affordable. The Human Connectome Project was first to distribute MEG data on a large scale from a subsample of its cohort, along with extensive multimodal MRI, behavioral and genetic data. With about 150 data volumes available, the Open MEG Archives (OMEGA) is the second-largest repository of resting-state MEG data, and it additionally contains T1-weighted MRI volumes of participants (Niso *et al.*, 2016). The recent CAM-CAN initiative features data from about 650 healthy participants ages 18–88, combined with multimodal MRI and extensive cognitive testing.

Larger volumes of data also enable new research tools. The present renaissance of artificial intelligence methods is boosted by access to such large data resources, and the augmented access to high-performance computing. Resorting to big-data tools and methods is becoming increasingly strategic in systems and clinical neuroscience, especially with neuroimaging; data analysis pipelines have grown in sophistication, and data volumes have inflated concurrently with the augmented spatial and temporal resolution of instruments. We have already put forward the scientific motivation to combine multiple data types (genotypes, imaging and behavioral phenotypes, clinical data, tissue samples, etc.,), which transforms every research participant's record in a big-data volume. In parallel, community awareness is now growing toward expanding the curated value and lifetime of data collections in public research. The increasing number of open data-sharing initiatives emphasizes and incarnates stronger educational, economical, ethical and societal values in science.

For the neuroimaging and electrophysiology community, this represents a vital opportunity to validate methods more thoroughly and to overcome the limitations of small-sample, low-powered, and consequently poorly reproducible studies that are eventually detrimental to the credibility of the field. At the same time, it should be kept in mind that the concepts of statistical power and sampling refer not only to the number of

participants, but also to the number of time points sampled from a given individual. High-density, in-depth longitudinal data from a relatively small number of individuals transitioning from childhood into adulthood may carry great heuristic value and inform the design of large-scale studies with larger samples of individuals.

Other options for large-scale data acquisition include use of clinical data and new technologies. Clinical institutions often have databases and large repositories of data from individuals with and without diseases that could be repurposed for research. New technologies such as ecological momentary assessment (EMA) tools that are smartphone-based, or wearable technologies that permit open-field measurements of EEG, electrodermal responses, and eye-tracking can record the subjects' current behaviors and experiences in real time, and in their typical everyday environments.

Ensuring the reliability of results in these studies is also important. Study design should include both confirmatory and exploratory outcome measures in a single cohort, to allow for replication of previous results and validation of study methodology. Statistical tools for longitudinal studies that efficiently combine confirmatory and exploratory approaches are available (Brandmaier *et al.*, 2015). Adolescent longitudinal studies can particularly suffer from biases and hidden variables related to environmental factors. Therefore, additional qualitative or quantitative data related to lifestyle that are relevant to the adolescent should be obtained, including interactions with parents and peers, school performance, risk- and sensation-seeking behaviors, romantic/sexual experiences, and substance use/addiction.

II. Animal Model Studies

Animal models of adolescence should be used in parallel with human studies because they provide the opportunity to actively interact with neural networks and help to establish arrows of causality, which is often impossible in research involving human subjects for ethical reasons. It must be acknowledged, however, that determining chronological ages that correspond to adolescence and adulthood across species is nontrivial, especially when the duration of adolescence is radically different between species. In addition, developmental animal studies require that the animals have normal adolescent experiences, including social experiences with animals of the same and opposite sex. Such experiments call for development of more naturalistic ecological environments for lab animal breeding and housing, both for rodents and non-human primates.

For reasons similar to those described previously for human studies, longitudinal study design should be used for experiments in animal models, with efforts to look for inflection points and trends across multiple measures that resemble patterns of human adolescence (see Figure 1). Behavioral assessments of adolescent animals can also be challenging, as many human behaviors do not have identifiable corresponding behaviors in animals. As such, there is a suggestion in the field that use of social non-human primates, such as marmosets, may provide better assessments of cognition and certain inter-individual interactions.

The specific benefits of animal models include improved spatiotemporal resolution for electrophysiological data, with the opportunity to record local field potentials, multiunit activity, and even action potentials from

individual neurons across multiple brain regions simultaneously. There is also improved access to deep and mesial structures, such as the hippocampus, medial prefrontal cortex, and striatum, brain regions that are thought to undergo major modifications in the adolescent period. Furthermore, it is possible to interact with specific cell types and neural circuits in these animals using a combination of viral vectors, RNAi technologies, inducible mouse knockout/transgenic lines, optogenetics, designer receptors exclusively activated by designer drugs (DREADDS), and responsive neurostimulation. Such methods have already been used in adolescent animals to help establish brain processes that are causal to expression of a specific phenotype (Niwa *et al.*, 2010; (Cho *et al.*, 2015).

III. Neural Network Modeling Studies

A currently under-explored method in developmental neuroscience is neural network modeling. Artificial neural networks can now attain or surpass human level performance in various cognitive tasks (Esteva *et al.*, 2017). It may therefore become possible to gain insights into how brains mature by investigating how these networks learn. For instance, training deep neural networks with specific characteristics, such as reinforcement learning with a transient heightened sensitivity to rewards (see Section 2), may serve as a testing ground for exploring forms of adolescent plasticity.

Relatively simple implementation of machine-learning decoding techniques in imaging or multichannel electrophysiology for multidimensional signal classification show impressive applications, such as in identifying early components of visual object categorization and in tracking the temporal organization of spatial patterns of brain activity or that of a mnemonic template in the context of perceptual decisions (Myers *et al.*, 2015). The fact that these methods are, for now, independent of signal models make them an attractive complement to researchers for rapid evaluation of their data—for example, to assess the presence and spatiotemporal topography of effects between experimental conditions or cohorts. Representations similarity analyses were extended to the joint processing of MEG brain data with the outputs of a deep neural network, respectively obtained from and trained on the same visual categorization task (Cichy *et al.*, 2016) This innovative and multimodal approach may allow neuromimetic models to refine, and even discover, new principles of brain function applicable to developmental stages "as the adolescent machine learns."

We can also anticipate that artificial agents may soon be able to capture subtle combinations of behavioral and peripheral markers from psychiatric patients, without the interpersonal challenges such patients experience with human interventions. We may also extrapolate that AI agents, in the form of robots or augmented-reality applications, may become part of the palette for future treatment interventions in neuropsychiatry. Of course, current robotic systems are still, technically, in their "infant development phase" with robotic engineers able to implement only infant-level capacities and infant learning into embodied systems. As this technology inevitably progresses and society increasingly embraces virtualized forms of interactions, we should be prepared to incorporate artificial intelligence into our tool kit for evaluating human development.

Section 4: Testable hypotheses of abnormal brain coordination in adolescence

Research into both the physiology and pathology of the brain provide complementary views of neural function. Often, features of clinical disorders can shed light onto the underlying physiologic processes that have been deranged. Similarly, mechanisms of normal brain processes can provide a starting point to understanding how neuropsychiatric diseases arise and how to most effectively treat them. This concept is particularly relevant to late adolescence, which is characterized by both the emergence of several disorders, but the remittance of others.

During late adolescence, mental disorders such as schizophrenia and affective disorders emerge, raising the question of the underlying biological vulnerability and mechanisms that confer risk for psychopathology. One possibility is that the nonlinear maturational changes in neural systems during this age period provide windows of vulnerability that either a) provide favorable conditions for the emergence of an already existing developmental vulnerability mediated by an earlier developmental insult and/or genetic risk; or b) lead to an expression of psychopathology due to an interaction with environmental events, such as the changing social landscape and increases in social stress.

Among the possible neural mechanisms undergoing profound changes during late adolescence are brain coordination in emotion regulation networks, reward-mediated predictions, and large-scale phase-synchronization. On a phenomenological level, there is close relation between the changes in these networks and disorders involving disturbances in affect (mood disorders, personality disorders), reward (psychosis and substance abuse) and cognition (schizophrenia and bipolar disorder), which tend to emerge during this period. In line with structural evidence (Douaud *et al.*, 2014), it is conceivable that developmental modifications in these circuits may have a causal role in the emergence of specific domains of psychopathology during the transition from adolescence to adulthood.

Adolescence and early adulthood also see the emergence of several genetic or presumed genetic epilepsies, including autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), autosomal dominant partial epilepsy with auditory features (ADPEAF), and familial mesial temporal lobe epilepsy (MTLE). These epilepsies are localized by seizure semiology and epileptiform electrophysiological patterns to frontal and temporal cortices, regions that are later to mature, and undergo more profound changes during adolescence. Although the mechanisms contributing to this developmental stage-specific expression of epilepsy are mostly unknown, in some cases where human genetic mutations have been identified, progress is being made. Many patients with ADNFLE have mutations in the genes coding for neural nicotinic acetylcholine receptors. Conditional mouse models that can reversibly express similar mutations have demonstrated that expression of the abnormal receptor must occur in the juvenile state for epilepsy to result; expression solely in adulthood is insufficient to cause the clinical phenotype (Douaud *et al.*, 2014).

Different childhood epileptic syndromes have a high rate of remittance by late adolescence, suggesting that there are physiologic or compensatory developmental processes that can facilitate “normalization” of brain function. Epilepsies that are likely to remit include Panayiotopoulos syndrome, Gastaut syndrome, and benign

rolandic epilepsy of childhood (BREC). The abnormal networks in these syndromes are localized by seizure semiology and epileptiform electrophysiological patterns to the occipital and sensory/motor opercular cortices, regions that are earlier to mature during development and less affected by structural and functional changes during adolescence. The mechanisms underlying remittance of epileptic disorders are unknown, but merit further investigation. Taken together, these observations lend support to the notion that the normal developmental processes of late adolescence determine the patterns of dysfunction and recovery that can be expressed during this phase. Such a hypothesis would need to be supported by multimodal prospective longitudinal investigations of patients who are at high risk for development of neuropsychiatric disease, actively experiencing symptoms of the disease, and after remittance or effective treatment, if applicable. Given the ability to noninvasively assay dynamic brain coordination using electrophysiological techniques, further consideration of how these methods could be applied to neuropsychiatric disorders is warranted.

We propose that electrophysiology geared to monitor dynamic brain coordination is a key methodology to investigate the onset, evolution, and remittance of neuropsychiatric disorders. There is emerging interest in human electrophysiology to study the typical brain rhythms (theta, alpha, beta, gamma, etc.,) as coupled and interdependent, rather than separate, expressions of physiological mechanisms. Measures of cross-frequency interactions, originally demonstrated in rodent electrophysiology, such as phase–amplitude coupling (PAC), can now be obtained in human noninvasive data (MEG or EEG (Baillet, 2017)). For instance, there is growing evidence that the human resting-state ongoing activity is structured by bursts of gamma to fast-gamma activity, whose amplitude is modulated by the phase of slower oscillations in the delta to alpha ranges (Florin & Baillet, 2015) The slower delta to alpha rhythms mark the net excitability of cell assemblies consisting of slow and fast inhibitory (SI and FI, respectively) and excitatory (E) cells (Buzsaki, 2006). Holistic theoretical frameworks for the organization of brain rhythms, such as the model of synchronized gating and others, consider brain network formation and communication to be enabled by the phase alignment of these cycles between regions (Fries, 2005; (Florin & Baillet, 2015). This can be facilitated by the mechanism of dynamical relaying via the thalamus or cortical hub regions.

While gamma bursts could contribute to bottom-up signaling, beta bursts could manifest top-down modulations generated by upstream regions and thereby contribute to the implementation of contextual predictive inference of input signals. We can anticipate that the later phases of maturation in the adolescent brain, especially concerning the prefrontal areas and associated white fiber tracts, could be evaluated indirectly by evolving expressions of cross-frequency coupling in healthy development and the early onset of syndromes that affect, directly or indirectly, cell excitability. Such a dynamical scaffold, among others possible, helps formulate testable hypotheses inspired by preclinical/developmental animal models, using human scalp signals. In short, a global roadmap for MEG/EEG electrophysiology and imaging to build on these recent and still relatively sparse advances would ideally consist in (i) further clarifying the physiological principles structuring the local-to-global dynamics of neural oscillations, (ii) defining measures of regional activation and inter-areal communication in brain systems that are driven by these biological principles (iii) using these measures to survey the dynamical repertoire of the resting brain, which remains

largely uncharted, and (iv) understanding how sensory inputs interact with this repertoire, enabling functional integration and eventually behavior. Approaching future MEG/EEG research with this plan would open considerable perspectives—for instance, by verifying that an aberrant repertoire of brain-dynamics phenotypes are expressed in diseases. This would enable a new generation of electrophysiological markers of pathology and eventually new forms of intervention.

Section 5: Brain network approaches to diagnosis, treatment, and prevention of adolescent brain disorders

Neuropsychiatric diseases that emerge in adolescence can have profound and long-lasting adverse consequences for the affected individual and their interactions with society. Identifying reliable biomarkers of these diseases that can facilitate early detection and appropriate treatment to mitigate these effects. Equally important is ensuring that these diagnostics and therapeutics can be disseminated broadly to the community to reach all those at risk. Evidence from epidemiologic studies of patients with schizophrenia and those with epilepsy indicate that delayed treatment often results in increased difficulty with later control of the disease symptoms. The concept of kindling is recognized in epilepsy across development, wherein the frequent occurrence of seizures can decrease the threshold for further seizures. It may be of clinical relevance to consider whether a similar concept may apply to psychiatric disorders, especially during adolescence when networks affected are likely undergoing modifications that could make them more plastic to repeated abnormal cognitive or behavioral experiences (such as hallucinations, panic attacks, or rapid cycling of mood).

The quest for better diagnostics and therapeutics for disorders of adolescence is complicated by the fact that, as discussed previously, the neural circuits most likely to yield biomarkers of disease are the same circuits undergoing modification during normal adolescence. Therefore, biomarkers in this developmental phase may not be stable, but instead be modulated by the specific time during adolescence in which they are assayed. Coupled with the fact that it is difficult to determine where any individual is on a developmental trajectory by obtaining data at a single time point, the notion of a biomarker may have to be modified to effectively apply to adolescence. Furthermore, it has been shown in numerous instances that cognitive abilities and symptoms, and likely network properties that underlie them, follow a lognormal rather than bimodal distribution of occurrence in the population. This idea is supported by the typical requirement for functional impairment as part of diagnostic criteria for psychiatric disorders, acknowledging that unless certain symptoms or traits are pervasive enough to impair the individual in their daily life or interaction with society, they may exist within a spectrum of normality. As such, determining the threshold of abnormality for any given biomarker will likely remain challenging.

Adolescence also poses particular issues for therapeutic approaches. Certain behaviors and cognitive states, such as risk taking and embracing of the contra-hedonic state, are normative and serve a purpose during adolescence, despite being maladaptive in other life-stages. Therefore, it is key to use developmental-specific norms, and to avoid attempting to over-normalize behaviors that are likely necessary for proper maturation

of experience-dependent circuits. Current treatments for many neuropsychiatric disorders carry side effects that can themselves affect brain and body health. For instance, antipsychotics used for schizophrenia can induce a metabolic syndrome that adversely affects cardiovascular health. Anticonvulsants used for both epilepsy and mood disorders can be associated with cognitive dysfunction, among other systemic effects. It is possible that use of these agents during adolescence poses additional unrecognized hazards, as has been identified with the suicide risk associated with use of certain antidepressants in adolescents but not adults, and the decrease in IQ associated with prenatal exposure to the anticonvulsant, valproic acid.

Given these issues, we suggest that neuropsychiatric disorders during adolescence may need to be reframed based on different combinations of symptoms (behavioral phenotypes) that can more directly be attributed to dysfunction of specific networks. For example, the Diagnostic and Statistical Manual of Mental Disorders largely describes mental disorders as cross-sectional clusters of symptoms, prioritizing clinical reliability over biological validity. This approach impairs ability to closely link pathogenic mechanisms with the disorders. To address this challenge, the NIMH has proposed the Research Domain Criteria (RDoC) (Insel *et al.*, 2010). This initiative dissects mental disorders according to a matrix of dimensions or phenotypes with presumed, well-defined biological etiology, providing a scaffold for research to understand disease on the level of genes, molecules, synapses and ultimately dynamic brain coordination (Casey *et al.*, 2014).

In addition, such an approach would allow investigators to look for biomarkers of specific neurologic or psychiatric symptoms in biologically plausible anatomical networks. Rather than requiring that any particular biomarker be sensitive and specific for one clinical disorder, a combination of biomarkers could be used to define a disorder, potentially with the existence of some biomarkers in isolation being within the normal spectrum. Assessment of treatment response could also then be focused on specific symptoms and changes in features of the associated biomarker, with objective and clinically relevant outcome measures.

To better understand, diagnose and most effectively treat the atypical neuropsychiatric brain, it is important for future research to further target the various neural network dysfunctions identified. General network markers for neuropsychiatric pathologies have been discovered and described in detail for the adult brain (Ribary, 2014). Earlier findings demonstrated that in several neurological and neuropsychiatric populations, (i) resting-state peak-power oscillatory frequency was persistently slowed from an alpha to a theta rate, (ii) theta and gamma power were persistently increased, and (iii) persistent cross-frequency coupling was observed among theta and gamma rhythms (Llinas *et al.*, 1999). This is understood to result from either a deafferentation of thalamus (i.e. chronic pain) or an excess of inhibition of thalamic activity (i.e. Parkinson's Disease). In addition, extensive review into the current human and animal literature further provided possible clues for the underlying neurophysiological mechanisms (Doesburg, 2015). To the best of our knowledge, such studies have not been performed during adolescence, but their findings may provide a possible neurophysiological framework for studying such typical or atypical developmental trajectories in network abnormalities.

Once systems level biomarkers for network dysfunction can be identified, we can begin to think about novel approaches to therapeutics (Figure 2). Evidence suggests that cognitive or environmental interventions can potentially retrain dysfunctional neural networks. Computerized cognitive training in patients with schizophrenia appears to ameliorate some symptoms of the disease and normalize associated biomarkers (Subramaniam *et al.*, 2012). Similarly, the ventral hippocampal lesioning model of schizophrenia can be rescued by environmental strategies in rodents. Cognitive behavioral and other therapy methods likely also have at least some basis in retraining neural networks subserving higher cognitive functions. Identifying the networks that are dysfunctional will allow targeted cognitive interventions that are more likely to be successful. It is likely that such interventions will be insufficient in isolation to treat moderate to severe manifestations of neuropsychiatric disorders. However, for certain cognitive disorders, such as attention deficit disorder, there is no clear diagnostic line between normal and abnormal function. This uncertainty leaves a "gray area" with a large proportion of adolescents who could certainly benefit from improved cognitive performance, but where the risk benefit analysis of pharmacological therapy is not positive. One option in this case is to develop programs that emphasize metacognition (learning to recognize brain mechanisms in one's own behavior) and cognitive strategies (a cognitive "toolkit") to guide adolescents toward more efficient top-down stabilization of their brain dynamics. Of course, we should stay away from any attempt to normalize brain activity according to arbitrary standards and value scales, but instead, provide the individuals means to increase his/her range of options at the behavioral level. The ATOLE program in France, led by one of the contributors (JPL) is an example of such a program, among others currently in operation (e.g. "attentix" in Canada).

If specific networks could be identified as dysfunctional, treatment with direct neural network perturbation could also be employed. Responsive scalp electrical stimulation, deep brain stimulation, and repetitive transcranial magnetic stimulation are currently being used to treat a variety of neurologic diseases, including epilepsy, depression, movement disorders, and stroke. Although the mechanisms of benefit and the optimal stimulation parameters remain unknown, modest to impressive behavioral and clinical benefit can be observed (Albouy *et al.*, 2017). As our understanding of the pathophysiology of these neural networks progresses, it should be possible to define better, more focused therapeutics. Such approaches could be particularly effective during adolescence, when network plasticity may be more easily invoked.

Outlook

Effective transitioning from adolescence to adulthood is a basic component of a functional society, and better understanding of the neurobiological underpinnings of this change could have far-ranging benefits. We propose that the adolescent brain undergoes numerous nonlinear modifications that set it apart from both the child and adult brain. These changes are characterized by a predilection for specific forms of plasticity that predominantly affect neural networks involved in higher cognitive and emotional processes. There are multiple methods at our disposal to interrogate the adolescent brain, but dedicated and standardized

initiatives are required to collect the relevant longitudinal data. A focus on dynamic brain coordination across multiple modalities may allow us to better assay the neurophysiologic processes of typical adolescent development, and identify neural network level biomarkers and therapeutics for the neuropsychiatric diseases that characteristically emerge during this phase. Perhaps then we will be able to view adolescence as a double positive rather than a double negative: more adventurous, social, and cognitively mature than children, and not yet under the inevitable influences of senescence.

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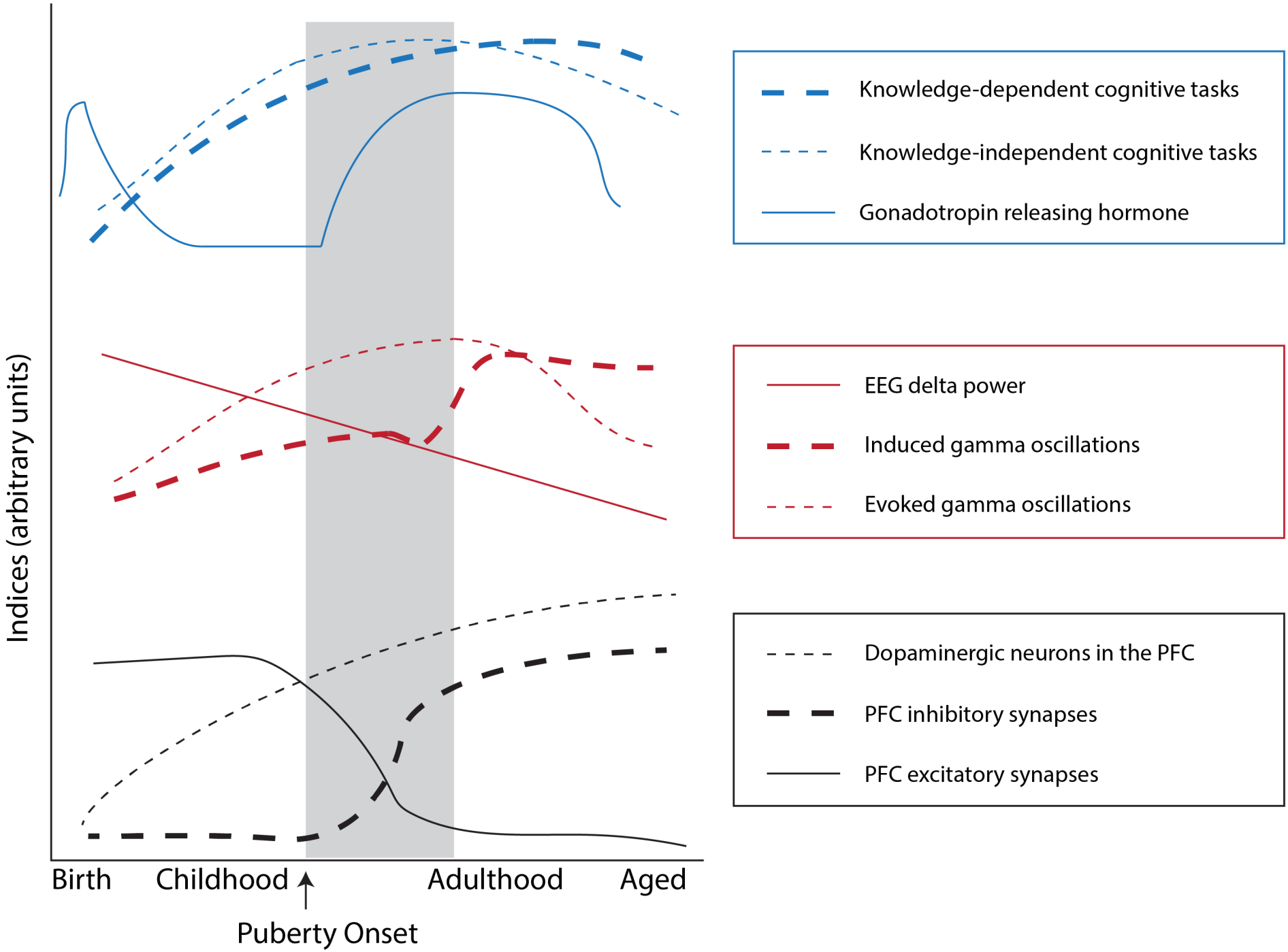
Figure Legends

Figure 1: Variable trajectories of multidimensional neurobiological measures that can define a window for the transition from adolescence to adulthood. Molecular measures in black, network level measures in red, and functional measures in blue. Grayed out window defines putative period of late adolescence.

Figure 2: Separation of neuropsychiatric disorders into dimensions corresponding to functional neural networks may provide insight into novel biomarkers and treatment approaches.


Indices (arbitrary units)
Birth
Childhood
Puberty Onset
Adulthood
Aged
Knowledge-dependent cognitive tasks
Knowledge-independent cognitive tasks
Gonadotropin releasing hormone
EEG delta power
Induced gamma oscillations
Evoked gamma oscillations
Dopaminergic neurons in the PFC
PFC inhibitory synapses
PFC excitatory synapses

Disorder	Distinct Clinical Features							
Schizophrenia	A	B	C					
Bipolar Disorder 1			C		E	F		
Bipolar Disorder 2				D	E	F		
Major Depressive Disorder			C			F		
Frontal Lobe Epilepsy			C				Y	Z