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Aдриене M. Beltz

University of Michigan

Department of Psychology

Ann Arbor, MI 48109

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Correspondence concerning this article should be addressed to Adriene M. Beltz, University of Michigan, Department of Psychology, 2227 East Hall, 530 Church Street, Ann Arbor, MI 48109; phone: 734-647-6788; e-mail: abeltz@umich.edu.

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Connecting Theory and Methods in Adolescent Brain Research

Excitement surrounds network approaches and interpretations in adolescent brain research. There is the mentalizing, socio-emotional, cognitive control, frontoparietal, and cinguloopercular network, not to mention the incentive processing and ventral affective system, socioaffective circuitry and the prefrontal-limbic and cortico-subcortico connectivity (Blakemore, 2008; Casey, Getz, & Galvan, 2008; Fair et al., 2009; Somerville, 2013; Steinberg, 2008; Strang, Chein, & Steinberg, 2013). This move away from “blobology,” or studies of cognitive subtraction in which functionally segregated brain regions are considered responsible for certain behaviors, and toward investigations of the interconnections and cross-communication among brain regions is imperative and exciting. It mirrors the true functioning of the brain, and the current thinking in neuroscience (Smith, 2012).

Unfortunately, the analysis approaches being utilized in many empirical examinations of adolescent brain connectivity do not reflect the quantitative sophistication of the broader field of neuroscience (Gates & Molenaar, 2012; Smith et al., 2011). This is particularly evident in analyses of task-based blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) data (for complementary reviews, see Goldenberg & Galvan, 2015; Peper, van den Heuvel, Mandl, Pol, & van Honk, 2011; Stevens, 2016). Yet, some theories and many hypotheses concern the coordinated coactivation of neural responses to specific stimuli and require sophisticated task-based connectivity analyses. Thus, there is a mismatch between theories of adolescent brain function and the quantitative methods used to test those theories.

The aim of this paper is fourfold. First, the disconnect between theories and methods in research on adolescent brain development is illustrated with respect to the dual systems model. The dual systems is used as an exemplar due to its prominence in the literature and the relatively common misalignment of its theoretical tenets and analytic operationalization (Shulman et al., 2016), but most arguments generalize to other theories of adolescent brain development. Second, some key task-based connectivity approaches that have been applied to adolescent brain function (i.e., seed-based correlations, psychophysiological interactions, and dynamic causal models) are reviewed, and their strengths and weaknesses are discussed. Third, a connectivity approach that holds promise for adolescent brain research, namely extended unified structural equation models, is introduced. Fourth, a simulation study is conducted to showcase how theory and methods can be integrated with respect to the dual systems model using this new method.

The Theory-Methods Disconnect and the Dual Systems Model

The dual systems model of decision-making is a well-known theory of adolescent brain development dominated by conversations about connectivity. It has been used to explain risk-taking associated with adolescent increases in vehicular accidents, pregnancy, and crime, to elucidate adolescent-emergent neuropsychiatric disease, and to influence policy concerning the driving age and judicial sentencing (Casey et al., 2008; Dahl, 2008; Paus, Keshavan, & Giedd, 2008; Steinberg, 2009). The basic heuristic is that risk-taking results from bottom-up reward processing of appetitive stimuli that trumps top-down inhibition; this is exaggerated in adolescence versus childhood and adulthood due to normative trajectories of regional brain development (Casey et al., 2008; Shulman et al., 2016; Steinberg, 2008, 2010). The original theory generally purported that neural circuitry underlying affect and reward matured before the circuitry underlying cognitive control, but the theory has become increasingly nuanced over time, incorporating information about developmental trajectories of different brain regions, molecular neurodevelopment (e.g., neurotransmitters; Teicher, Andersen, & Hostetter, 1995), and the operational definition of “maturation.”

Although there is variation, the affective circuitry generally includes the subcortical and dopamine-sensitive striatum and limbic system, particularly the nucleus accumbens (NAcc), and sometimes the medial prefrontal cortex (MPFC) (Casey et al., 2008; Steinberg, 2008). This network is thought to develop in an inverted U-shaped pattern in concert with puberty (Dahl, 2004; Steinberg, 2010). The cognitive control circuitry generally consists of the anterior

cingulate cortex (ACC) and parietal regions, but the PFC is key (Casey et al., 2008; Steinberg, 2008). This network is thought to develop linearly in concert with age (Dahl, 2004; Steinberg, 2010). Due to the different developmental trajectories of the affective and cognitive control networks, the latter has little influence on the former in arousing contexts, especially those concerning monetary or social rewards in early adolescence. Thus, network connectivity is important to the dual systems conceptualization of adolescent brain development.

There is support for the dual systems model from empirical work (including a meta-analysis) taking a functional segregation approach with standard general linear model (GLM) analyses of group differences (reviewed in Shulman et al., 2016; Silverman, Jedd, & Luciana, 2015). For example, Chein and colleagues (2011) showed that adolescents took more risks than adults in a driving simulation when accompanied by peers than when alone, and that heightened brain responses in the ventral striatum and orbitofrontal cortex (OFC) subserved this behavior. Adolescents also had less activity in brain regions implicated in cognitive control, such as frontal and parietal regions, when they took risks. Another example comes from Galvan et al. (2006), who reported that adolescents had greater functional responses in the NAcc to large monetary rewards than did children and adults, but the extent of their OFC activation was in between that of children and adults. Results of both studies are consistent with the dual systems model, showing an inverted U-shaped pattern in reward-related regions and linear change in cognitive control regions across development, but two concerns arise. The first is that the studies disagree on the role of the OFC, with Chein et al. (2011) considering it a reward region and Galvan et al. (2006) considering it a cognitive control region. The second is that GLM analyses do not permit conclusions about the interplay between these networks, so Chein et al. (2011) likely go beyond their data when they conclude that “these systems contribute to decision-making in an interactive fashion” (p. F1). Fortunately, task-based connectivity analyses can overcome these concerns by showing how a brain region (e.g., OFC) simultaneously relates to others across experimental conditions, and by explicitly modeling the interplay among brain regions in different networks.

Connectivity analyses also have the potential to address critiques of the dual systems model. The model has been criticized for downplaying individual differences (Casey & Caudle, 2013), with one volumetric study showing that affective regions (NAcc and amygdala) indeed reached volumetric stability before cognitive control regions (PFC), but that the mismatched timing did not relate to risk-taking behavior (Mills, Goddings, Clasen, Giedd, & Blakemore,

2014). Because the size of a brain region is not necessarily indicative of its synchronized activity with other brain regions, functional connectivity analyses largely circumvent this critique.

Concerns have also been expressed about post hoc explanations for regional brain activation in the dual systems model, with immaturity being tied to adolescent hyper and hypoactivity of the PFC and NAcc (Bjork et al., 2004; Pfeifer & Allen, 2012). In response, some have argued that inferences can only be made with respect to characteristics of the task used in a study, and not to the dual systems model per se (Strang et al., 2013). Regardless, both sides agree that functional connectivity analyses can inform this heated issue.

Finally, the dual systems model, despite being an explanation for normative development, was initially considered to be a deficit model, implying that adolescent differences from children and adults are somehow detrimental (Dahl, 2004; Pfeifer & Allen, 2012). But, if the adolescent brain is reorganizing, as evidence from human histological studies and animal experiments suggests (Huttenlocher & Dabholkar, 1997; Sisk & Zehr, 2005), then the teen years also pose a great opportunity for enhancement. Connectivity analyses are in a unique position to inform this issue, as they reflect covariation among – not levels of activation in – brain regions. They reveal characteristics of neural systems underlying behavior, potentially providing insight into novel mechanisms of intervention. For instance, they show how the activity of one brain region could be modulated by the activity of other, connected regions (not just through direct stimulation).

Thus, connectivity analyses have significant potential for providing insight into adolescent functional brain development, as demonstrated by research on the dual systems model. Assessing task-based connectivity would extend findings from standard group differences analyses, speak to criticisms, and serve as a consequential test of the theoretical model. Just as there is a mismatch between the developmental trajectories of the affective and cognitive control regions in the adolescent brain, there is a mismatch between the theory and methods used to understand adolescent brain development. Task-based connectivity analyses can reduce that gap.

Methods Used to Study Adolescent Brain Connectivity

The promise of task-based connectivity methods for understanding adolescent brain development has been realized by a handful of studies, primarily representing three analysis methods: Seed-based correlations, psychophysiological interactions, and dynamic causal models. The methods are reviewed below. For each, a description is given, an exemplary study on the dual systems model is described, and a critique is offered.

Seed-based Correlation Analyses (SCAs)

Correlations among voxels or brain regions of interest (ROIs) can be used as a measure of connectivity (Sporns, 2011). In fMRI studies, these analyses are typically applied by extracting the BOLD time series from a seed region and correlating it with all other voxels in the brain by entering it as a regressor in a GLM. The seed region can be selected in multiple ways, including a priori specification based upon past research or post hoc selection based upon sample-specific neural responses to a task. SCAs capture the synchrony among the seed region and other brain regions, or how activity in the regions rises and falls in concert.

SCAs produce undirected functional connectivity maps (Friston, Moran, & Seth, 2013; Sporns, 2011). The relations are undirected because they cannot specify how two regions are related (i.e., whether region A predicts region B or vice versa); they just indicate the presence of a positive or inverse association. Thus, causality cannot be inferred from the maps, as, for instance, a third region could be a cause of the relation between two others. The connectivity is functional because the relations show statistical dependencies in the measured BOLD signal.

The most common applications of SCAs in adolescent brain research are to resting state fMRI data (i.e., not to task-based data; Fair et al., 2009; Stevens, 2016), but SCAs nonetheless have been used in empirical investigations related to the dual systems model (e.g., Christakou, Brammer, & Rubia, 2011; Hare et al., 2008). For instance, in a landmark study Hare and colleagues (2008) assessed top-down control of bottom-up emotional responses to fearful faces in children, adolescents, and adults. The amygdala (part of the affective network), which had greater activation in adolescents than in children and adults, showed habituation across the task, and was used as a seed region in SCAs. Results showed that the amygdala was positively associated with the ventral PFC, and that the strength of the association was inversely related to habituation. This finding is important theoretically and methodologically. Theoretically, it aligns with the dual systems model, in that there is limited top-down connectivity when affective reactivity is high. Methodologically, it demonstrates how brain connectivity can be examined in the context of a task, and how it can be linked to other brain and behavioral measures.

Despite providing insights like this, SCAs have significant limitations. First, they only reveal undirected connections. With respect to the findings reviewed above (Hare et al., 2008), it actually cannot be determined whether ventral PFC activity predicts amygdala activity in a top-down fashion or whether the amygdala predicts ventral PFC in a bottom-up fashion. Second,

SCAs only assess instantaneous connections, that is, activity measured in different brain regions at the same volume, or time t . This is problematic because there are temporal dependencies within and between brain regions in fMRI data. Failing to account for them confounds results and substantive interpretations (e.g., Woolrich, Ripley, Brady, & Smith, 2001). Third, it is difficult to incorporate information about behavior or task conditions into SCAs, especially without concatenating disparate sections of the BOLD time series, and distorting the meaning of t . Partly for this reason, most applications of SCAs have been to resting state data (Stevens, 2016). Although there is evidence for correspondence between some resting state and task-based networks (e.g., the default mode network), this is not the case for reward circuitry (Smith et al., 2009); even if it were, it is unclear how the correspondence changes with development. Thus, an interesting question for future research concerns the extent to which SCAs of resting state data can be used to inform network analyses of task-based data related to the dual systems model.

To summarize, SCAs have moved research on adolescent brain development in the right direction – away from functional segregation and toward neural integration. But, they provide a relatively poor match to theory, mapping only undirected contemporaneous connections and failing to explicitly model network effects of task conditions. Other methods are needed. One option is to include task-related variables in the analysis with psychophysiological interactions. Psychophysiological Interactions (PPIs)

Conceptually, PPIs are SCAs that explicitly model how psychological variables, such as task conditions or behavior, modulate brain connectivity (Friston et al., 1997). They show increases in connectivity between brain regions that occur in a particular context. Like SCAs, PPIs require the selection of a seed region, determine which voxels or ROIs are correlated with that region, and produce undirected functional connectivity maps. Unlike SCAs, PPIs indicate whether and how the magnitude of the connections depends upon some psychological state, usually the experimental condition from an fMRI task¹. Thus, PPIs show perturbations of a distributed neural network that are due to an interaction between a physiological state (i.e., seed region) and a psychological condition (i.e., task) on activity across the entire brain.

PPI analysis is usually conducted within a GLM framework (for a tutorial, see O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). The physiological variable (e.g., BOLD time series of a seed region) is one regressor, the psychological variable (i.e., vector denoting a task condition) is the second regressor, and the element-by-element interaction between the two

variables is the third regressor. Results of interest come from the third regressor: Above the main effect of the seed region on other brain regions (as would be determined by SCAs) and above the main effect of the task on brain regions (as would be determined by GLMs), does the connectivity between the seed region and other regions change during the task? Even though regressions speak to statistical prediction, PPIs produce undirected functional connectivity maps because the direction of prediction is reversible. Results between two regions are equivalent regardless of which region is used as the seed.

PPI analysis is among the most frequently used – if not the most frequently used – task-based connectivity method in adolescent brain research, including in investigations of the dual systems model. One recent study used a PPI analysis in a reinforcement learning paradigm to see if brain connectivity differed between adolescents and adults during episodic memory of images associated with positively-reinforced (correct) versus negatively-reinforced (incorrect) trials (Davidow, Foerde, Galvan, & Shohamy, 2016). The physiological variable was brain activity from a hippocampal seed region, and the psychological variable was memory for events. Results showed that in adolescents, but not in adults, there was connectivity between the hippocampal seed region and the putamen (part of the striatum) when remembering positive but not negative events. Moreover, this connectivity was associated with an independent measure of memory bias for positive events assessed outside the scanner, such that increased connectivity predicted increased bias only for adolescents. A PPI analysis was also used to examine connectivity during no-go trials in an affective faces paradigm to assess participants' ability to refrain from approaching appetitive (happy) stimuli (Somerville, Hare, & Casey, 2011). The physiological variable was brain activity from a right inferior frontal gyrus (IFG) seed region, and the psychological variable was withholding versus responding to happy faces. Results showed that adolescents had greater connectivity among the IFG and the ventral and dorsal striatum than did children or adults. Both studies (Davidow et al., 2016; Somerville et al., 2011) converge to highlight an important role for striatal connectivity in adolescence. PPIs were integral to theoretical inferences that could be drawn from these studies because they isolated connectivity underlying positive affective stimuli, and the dual systems model has specific hypotheses concerning approach-related brain networks.

Nonetheless, PPIs have limitations. Since they methodologically overlap with SCAs, they are restricted in some similar ways. For example, they only reveal instantaneous and undirected

connections. In the examples above, PPIs could not decipher whether striatal-based value assessments preceded hippocampal-cued memory (Davidow et al., 2016), or whether activity in the IFG directed activity in the striatum during inhibition (Somerville et al., 2011). In the best case scenario, these limitations restrict inferences. In the worst case scenario, they produce spurious results (see Gates, Molenaar, Hillary, Ram, & Rovine, 2010).

Furthermore, the three regressors used in PPIs are not orthogonal. The interaction is related to the time courses of the seed region and of the task. Because PPIs only model unique effects of the interaction, it is likely that some effects of interest go undetected. In other words, false negatives due to low statistical power are common. Related to this, PPIs are usually underpowered for event-related designs, and are best for block designs (O'Reilly et al., 2012).

Finally, PPIs are restricted to the sample or group-level. They generate the same network for every person in the analysis. Even though the strength of the connections can vary from person-to-person, and even though individual differences parameters can be extracted and related to behavior outside the scanner (as done in Davidow et al., 2016), the structure of the network is the same for everyone. Connections are only considered to be meaningful when they reach statistical significance at the group-level (e.g., in second level GLMs). This does not differ from standard GLM analyses or SCAs, but it is especially important to note in the contexts of connectivity and adolescent brain development, in which heterogeneity is the norm.

To summarize, PPIs are remarkable for their incorporation of psychological contexts into connectivity analyses, revealing how brain regions are related during experimental conditions. Because they were among the first network-based approaches to incorporate task effects, they are prevalent in the neuroscience literature, and the most widely used task-based connectivity approach in adolescent brain research. Nonetheless, they are constrained in their application; they are not optimal for event-related designs, and they do not afford inferences about time-lagged or directed connections among brain regions. They also fail to consider person-specific patterns of connectivity. Dynamic causal models overcome many of these drawbacks.

Dynamic Causal Models (DCMs)

DCMs have the same general goal as PPIs, that is, to determine how experimental conditions perturb a distributed neural network. In fact, in their original form for fMRI data (and the form in which they have been primarily applied in adolescent brain research), experimental input is required to estimate the network². This is because DCM blends control theory and

Bayesian statistics in a mechanistic and deterministic forward model, such that stimulus-evoked neuronal activity is projected across the brain as BOLD signal via structural connectivity and a hemodynamic response function (for elaboration and technical details, see Friston & Büchel, 2007; Friston, Harrison, & Penny, 2003). So, DCM assesses effective connectivity via biological propagation of a task input. Effective connectivity concerns the causal influence one brain region has on another (Friston et al., 2013). Because of the assumptions concerning neuronal firing made by DCMs, the connections between ROIs can be considered contemporaneous, occurring at an infinitesimal time lag and leaving no unmodeled dependencies in the data.

The effective networks generated by DCM differ from the undirected functional networks generated by SCAs and PPIs in several ways. First, the connections among multiple ROIs are estimated in a DCM network. In SCA- and PPI-based networks, only connections between a seed region and other regions are considered, leaving connections between non-seed regions undetected. Second, connections in DCM networks depict causal relations, showing the influence one ROI has on another. This causality is dependent upon time, space, and task (e.g., when and where in the brain the task exerts its influence). This differs from the undirected connections in SCA and PPI networks. Third, DCM networks are typically estimated in a confirmatory fashion², so researchers must specify a set of plausible network structures to be tested. This is in contrast to the network discovery approaches employed by SCAs and PPIs.

DCMs are usually conducted using Statistical Parametric Mapping software (Wellcome Trust Centre for Neuroimaging, London, UK; for accessible reviews, see Goldenberg & Galvan, 2015; Stephan et al., 2010). To start, a standard GLM is used to identify ROIs showing a task response. Next, the model space (i.e., set of plausible networks) is specified. DCMs require a task vector, the identification of all ROIs, and the specification of direct and modulating effects of the task and connections among ROIs. Lastly, DCMs cannot be evaluated by absolute model fit indices due to the way in which they are estimated, so results are evaluated by comparing the multiple specified models with Bayesian inference (Penny, Stephan, Mechelli, & Friston, 2004).

Most applications of DCMs to adolescent brain function concern bottom-up versus top-down control in basic cognition (e.g., Stevens, Kiehl, Pearlson, & Calhoun, 2007) or the characterization of clinical conditions (e.g., Diwadkar et al., 2012), but there is an exemplar study related to the dual systems model. In an attempt to understand the role of the thalamus in reward processing, Cho and colleagues (2013) examined effective connectivity in adolescents

and adults completing a monetary incentive delay task. Based on results of a GLM for trials in which participants gained money, the right NAcc and anterior insula were selected as ROIs along with the right thalamus. Seven models were tested, and Bayesian Model Selection and a preference to retain the model with the fewest constraints were used to select a nearly fully connected model for both adolescents and adults. As shown in Figure 1, network connections were differentially modulated by wins and losses for adolescents and adults, but parameter weights extracted from the modulated networks did not significantly differ between the groups. Thus, the results do not support the dual systems model even though they can be interpreted in terms of bottom-up and top-down processing of reward: During monetary gains, there is no connectivity between the insula (which uniquely contributes to reward-related decision-making) and the NAcc, but there is top-down connectivity of the insula directing the NAcc during losses.

Despite the benefits of DCMs, there are limitations. One concerns the confirmatory and comparative nature of the analysis, as it is typically applied. Researchers must indicate the ways in which ROIs are connected and how ROIs are affected by the task. This is a large model space to define, and researchers often do not have hypotheses about competing models, so they either fit models containing all possible connections (e.g., Stevens et al., 2007), or they fail to detect the optimal model. For instance, Cho et al. (2013) did not test a bottom-up model in which the NAcc predicted the insula, stating that the regions are not anatomically connected; but, functional connections could occur through indirect anatomical pathways. Moreover, simulation studies have bemoaned the countless models that can be fit in a single DCM study and the shortcomings of Bayesian model selection (Gates, Molenaar, Hillary, & Slobounov, 2011; Lohmann, Erfurth, Muller, & Turner, 2012).

Another limitation concerns the level at which inferences are often made in DCMs. Networks are typically estimated at the group-level³, as seen in the adolescent and adult networks in Figure 1. Individual-level parameters can be extracted from these networks depending upon a participant's deviation from the group average; these were compared between adolescents and adults in the study above (Cho et al., 2013). But, if a group is heterogeneous, then a group-level network structure may distort individual differences, and Cho et al. (2013) offered this as an explanation for their failure to find adolescent-adult differences.

To summarize, DCMs are significant improvements over SCAs and PPIs and hold potential for many research questions in adolescent neuroscience. They mathematically identify

effective networks among multiple ROIs by considering the interactions between experimental paradigms and neurobiology, including synaptic firing, structural connections, and hemodynamic responses. Because they are based on neuronal firing, their contemporaneous connections are unlikely to contain unmodeled temporal dependencies. But, in order to do this, DCMs make assumptions about neurobiology, and they require a degree of theoretical input that few researchers are prepared to give. The extent to which they accurately reflect sample heterogeneity is also unclear. Thus, in an attempt to advance understanding of the adolescent brain and to overcome some of the limitations of DCMs, a relatively novel exploratory model for person-specific brain connectivity is introduced in the next section.

Novel Method: Extended Unified Structural Equation Models (euSEMs)

Extended unified structural equation models combine many of the advantages of SCAs, PPIs, and DCMs (Gates et al., 2011). They create directed functional connectivity maps (Friston et al., 2013). The maps are directed because they show how activity in one ROI predicts activity in another ROI. They are functional because connections are determined by statistical dependencies in the observed BOLD signal. They have been used in other neuroscience applications (cited below), but not with respect to the dual systems model.

euSEMs hold significant potential for merging theory and methods in adolescent brain research. This can be seen by the ways in which they relate to and are distinct from SCAs, PPIs, and DCMs. First, euSEMs are a person-specific approach to connectivity mapping. SCAs, PPIs, and DCMs typically lose information by averaging across individuals or by calculating individual-level parameters as deviations from group averages. In order to reflect the heterogeneity inherent in fMRI and developmental data (Finn et al., 2015; Molenaar, 2004), euSEMs generate a network for each individual in a sample. These individual-level networks, however, contain group-level information, reflecting sample homogeneity and facilitating inference and generalization, when implemented in an algorithm called group iterative multiple model estimation (GIMME; Gates & Molenaar, 2012). The utility of GIMME for the analysis of data from heterogeneous neuropsychiatric samples has been established in studies on substance use, depression, and traumatic brain injury (Beltz et al., 2013; Hillary et al., 2011; Hillary, Medaglia, Gates, Molenaar, & Good, 2014; Nichols, Gates, Molenaar, & Wilson, 2014; Price et al., 2017). Thus, euSEMs implemented in GIMME provide a unique opportunity to ask and answer questions about individual differences in adolescent brain function.

Second, euSEMs represent an ROI-based exploratory approach to network discovery. GIMME uses a data-driven search to identify connections between ROIs and driving or modulating effects of a task⁴. It is as if euSEMs in GIMME combine the exploratory nature of SCAs and PPIs with the ROI- and task-based mapping of DCMs. This uniquely situates the approach in research on adolescent brain development. For example, had euSEMs been used in the DCM study above (Cho et al., 2013), they could have detected bottom-up connectivity between the NAcc and insula if it was meaningful for even one person, and they could have identified whether a subset of adolescents and adults differed in network characteristics.

Third, euSEMs use observed BOLD signal to statistically model contemporaneous and lagged connections among ROIs and driving task effects. This differs from SCAs, PPIs, and DCMs. SCAs and PPIs only model contemporaneous connections in the BOLD signal, and they are likely biased by unmodeled temporal dependencies (Gates et al., 2010). DCMs only model contemporaneous connections (which is reasonable since they are derived from an inferred neuronal signal occurring at infinitesimal lags). Thus, euSEMs have the potential to instigate new questions in adolescent brain development research concerning time series analyses of BOLD data without neurobiological assumptions. For instance, euSEMs could extend the PPI studies above (Davidow et al., 2016; Somerville et al., 2011) by revealing whether striatal activity precedes, coincides with, or follows activity in (sub)cortical ROIs during affective tasks.

euSEMs are in a class of models called structural vector autoregressions (Lütkepohl, 2005). The distinguishing feature of these models is their inclusion of both contemporaneous (structural) and lagged (vector autoregressive) connections⁵. euSEMs are unique compared to other structural VARs due to the way they are fit to the data. When implemented in GIMME (Gates & Molenaar, 2012), contemporaneous and lagged connections are iteratively added to an empty network using modification indices that specify how much model fit will improve if a given connection is added to the network (Sörbom, 1989). This iterative process is first conducted at the group-level by adding connections to all participants' maps if they will significantly improve model fit for some criterion (usually 75%) of the sample. The iterative process is then conducted at the individual-level by adding connections to the map of each participant (supplementing those added at the group-level) until the model fits well. After each level, non-significant connections are trimmed.

GIMME is an automated procedure conducted in standard software. There are currently two publicly-available versions, one (<https://cran.r-project.org/web/packages/gimme/index.html>) in R (R Core Team, 2015) and another (<https://www.nitrc.org/projects/gimme/>) in Matlab® (Mathworks, 2015) with a LISREL dependency (Jöreskog & Sörbom, 1992)⁶. Detailed instructions are provided in user manuals that accompany each version. Like DCMs, euSEM ROIs must be identified before running the analysis. Like DCMs and PPIs, task vectors must be provided in order to calculate the driving and modulating influences of experimental conditions on networks⁷. Unlike DCMs, the model space does not need to be specified because GIMME is data-driven. It estimates euSEMs in a pseudo-maximum likelihood framework (with results that are comparable to other estimation methods; Zhang, Hamaker, & Nesselroade, 2008), and builds networks that can be evaluated with standard model fit indices (e.g., comparative fit index).

The general steps in a GIMME analysis are depicted in Figure 2. Before submitting collected data to GIMME, they should be preprocessed using standard protocols. This includes motion correction, a critical issue in the analysis of developmental resting state data that has been shown to affect connectivity and to produce spurious group differences (Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012). The influence of motion on task-based networks, such as those derived by euSEMs, PPIs, and DCMs, however, has not been widely investigated, perhaps due to the assumption that time-locked stimuli prevent motion artifacts from propagating through a network.

After preprocessing, observed time series from ROIs are extracted. This is also done external to GIMME, and requires careful consideration of a variety of methodological issues (Stanley et al., 2013). Ultimately, it is the length of these time series (i.e., the number of volumes in a functional scan) that provide the statistical power for GIMME analyses because the networks are estimated at the individual-level. Power analysis for time series data is a topic of increasing interest, but straight-forward calculations and guidelines are limited (e.g., see Beltz & Gates, under review; Lütkepohl, 2005; Yaffee & McGee, 2000). As it true of all power analyses, sample size (number of time points) requirements depend upon the number of variables (ROIs) and size of the effects. The upper limit of the former is about 20 for GIMME, and the latter has particular implications for euSEMs estimated in GIMME because it is likely that modulatory task effects are small in size.

After running GIMME (as described above), network results can be linked to other psychological variables. For example, group differences (e.g., in age, gender, diagnosis, or condition) could be related to network features, such as the number of task effects or the magnitude of group-level connections or (e.g., Hillary et al., 2011). Moreover, graph theoretical metrics, such as network density or node degree (for other examples, see Sporns, 2011), could be correlated with behavior or estimated for the same individual across longitudinal scans, and then examined for developmental change (e.g., Beltz et al., 2013; Nichols et al., 2014). These analyses are conducted after GIMME using appropriate statistical tests (e.g., ANOVAs, growth curves), so effects of covariates and other predictors can be included using standard procedures. Finally, GIMME analyses could even be used to identify data-driven subgroups that cluster individuals based upon the similarity of their network features (e.g., Price et al., 2017).

Simulation: Extended Unified Structural Equation Modeling and the Dual Systems Model

A small simulation study was conducted to demonstrate the potential of euSEMs implemented in GIMME for developmental neuroscience, particularly the dual systems model. (Large-scale simulations to demonstrate accuracy and precision have already been conducted; Gates & Molenaar, 2012.) Simulations are paramount because they show how an analysis approach performs when conditions and outcomes are known, and thus, speak to the validity and reliability of results when conditions and outcomes are unknown (Smith et al., 2011). Therefore, the aims of this simulation were to illustrate how euSEMs via GIMME can: a) identify directed connections between brain regions and driving and modulatory task effects; b) create person-specific maps that accurately reflect individual differences; and c) operate without a priori information, that is, by using a data-driven approach to network building. These aims were accomplished with respect to the dual systems model by simulating data from adolescents differing in neurodevelopment while completing a monetary incentive delay task.

Methods

Data for 30 participants (10 early, 10 middle, and 10 late adolescents) were simulated according to a structural vector autoregressive model of the first order with three ROIs, one task condition, and 200 volumes acquired in 2s intervals. In other words, contemporaneous and lagged connections among three brain regions were created for BOLD fMRI data with a time to repetition (TR) of 2000ms, and the influence of a task on the network was considered. Based on related research (Cho et al., 2013; Hare et al., 2008), ROIs were the right NAcc (representing

affective processing), the right ventral PFC (representing cognitive control), and the right insula (representing affective appraisal), and the task concerned monetary gains, with trials occurring 33% of the time and their order fixed across participants.

Four connections were simulated at the group-level, that is, for all participants, as shown in Figure 3A. Three were autoregressive connections, which are common in fMRI research due to temporal dependencies in the BOLD signal (Beltz & Molenaar, 2015; Woolrich et al., 2001): The NAcc, PFC, and insula predicted themselves across time (i.e., at the next volume). The fourth was a contemporaneous driving effect of monetary gains on the NAcc (consistent with GLMs of adolescent affective processing; Chein et al., 2011; Galvan et al., 2006). Other simulated connections differed across participants. The 10 early adolescents had 2 additional individual-level connections reflecting bottom-up processing, as shown in Figure 3B. The NAcc governed the network, contemporaneously predicting the insula, and predicting the PFC during monetary gains (i.e., task modulation). The 10 late adolescents had 2 additional individual-level connections reflecting top-down processing, as shown in Figure 3D. The PFC governed the network, contemporaneously predicting the insula and NAcc regardless of monetary gains. The 10 middle adolescents had 2 additional individual-level connections reflecting their transitional state, as shown in Figure 3C. The NAcc predicted the PFC during monetary gains, and the insula contemporaneously predicted the NAcc reflecting the beginnings of top-down control. All connections had a standardized magnitude (β weight), ranging from 0.2 to 0.6.

Data from all 30 participants were submitted to an euSEM implemented in the Matlab version of GIMME (Gates & Molenaar, 2012). The model with a zero mean is defined as:

$$\eta_i(t) = (A_i + A_i^g)\eta_i(t) + (\Phi_{1,i} + \Phi_{1,i}^g)\eta_i(t-1) + (\gamma_i + \gamma_i^g)u_i(t) + (\gamma_{1,i} + \gamma_{1,i}^g)u_i(t-1) + (\tau_{1,1,i} + \tau_{1,1,i}^g)\eta_i(t-1)u_i(t-1) + \zeta_i(t),$$

where η is the simulated BOLD time series of the NAcc, PFC, and insula to be explained at time $t = 1, 2, \dots, 200$. A is the 3×3 matrix of contemporaneous connections, Φ_1 is the 3×3 matrix of lag 1 connections, γ and γ_1 are the 3×1 vectors of contemporaneous and lag 1 (respectively) driving effects of the task u , $\tau_{1,1}$ is the 3×3 matrix of modulating effects, that is, lag 1 connections between ROIs that are present during monetary gains, and ζ is the 3×1 error process with a mean of zero, diagonal covariance matrix, and no sequential dependencies. The superscript g reflects group-level connections present for all adolescents, and the subscript i reflects connections that were estimated for individuals (i.e., early, middle, and late adolescents).

Data in GIMME are fit via a model building procedure that utilizes Lagrange multiplier equivalents testing (described briefly above and in detail in Beltz & Gates, under review; Gates & Molenaar, 2012). The criterion for this study was set at 100%, meaning that a connection had to significantly predict variation in the maps of all 30 participants in order to be included at the group-level, and individual-level connections were significant at a Type I error rate of .01. Maps were deemed to fit well if two of the following fit criteria were satisfied (Brown, 2006): comparative fit index (CFI) $\geq .95$; non-normed fit index (NNFI) $\geq .95$; root mean squared error of approximation (RMSEA) $\leq .05$; standardized root mean residual (SRMR) $\leq .05$.

Results

GIMME generated 30 euSEM networks, one for each participant in the sample. They fit the data well, with mean indices of CFI = .99, NNFI = .98, RMSEA = .04, and SRMR = .03, and all connections were statistically significant at $p < .01$. As expected, each network contained four significant group-level connections, consisting of an autoregressive component for the NAcc, PFC, and insula, and a contemporaneous driving effect of the task (monetary gains) on the NAcc. These connections are indicated by red lines in the maps shown in Figures 3E-G.

The representative network for a simulated early adolescent is shown in Figure 3E. In addition to the group-level connections, the network contained two individual-level connections, consistent with the simulation. One is a contemporaneous connection from the NAcc to the insula (blue arrow). The other is a modulating connection from the NAcc to the PFC (blue diamond). All early adolescents had these connections, with two having additional connections of the task on the NAcc or insula, but the models still fit excellently without these effects.

The representative network for a simulated middle adolescent is shown in Figure 3F. Again, consistent with the simulation, the network contained two individual-level connections in addition to the group-level connections. As in the early adolescent data, there was a modulating connection from the NAcc to the PFC. There was also a contemporaneous connection from the insula to the NAcc. Nearly all middle adolescents had these individual-level connections. One was missing the modulatory effect, and another three had extra lagged connections, but in all cases, the models still fit well without these effects.

Lastly, the representative network for a simulated late adolescent is shown in Figure 3G. Results are consistent with the simulation, as the network contained two additional individual-level connections. Both are contemporaneous connections from the PFC to the insula and to the

NAcc. All late adolescents had these connections, with one having an additional connection of the task on the NAcc, but the model fit excellently without this effect.

Discussion

In a simulation designed to reflect a heterogeneous sample of adolescents completing a monetary gain paradigm, euSEMs implemented in GIMME accurately detected normative (group-level) and idiographic (individual-level) features of neural networks. Results were impressively consistent for a small-scale simulation of networks containing modulating (i.e., interaction) effects estimated separately for each person. At the individual-level, only 1 of 180 simulated connections was missed, and 12 false positives were found, but they were not essential to network fit. Moreover, they usually concerned lagged task effects inversely related to NAcc activity, which is a biologically plausible reflection of the hemodynamic response function, which stretches the effects of a task beyond the volumes to which the task is time-locked. So, these lagged inverse effects likely reflect some time-delayed feedback or temporal smoothing of the contemporaneous task effect on the NAcc. This simulation demonstrates the value of euSEMs and GIMME for understanding individual differences in adolescent brain connectivity, and the potential of the approach for answering novel research questions about adolescent risk.

Conclusions

Many theories about adolescent brain development concern networks, but their sophisticated hypotheses about connectivity are all-too-often investigated with GLM analyses of group differences. Thus, theory and methods are misaligned. The goal of the present work was to illustrate and to help reconcile this disconnect using the dual systems model as an illustration due to its ties to adolescent risk and resilience.

This work began with a review of three task-based connectivity methods that have been utilized in adolescent brain research: seed-based correlation analyses (SCAs), psychophysiological interactions (PPIs), and dynamic causal models (DCMs). The advantages and disadvantages of each approach as well as the ways in which they have informed the dual systems model were presented. SCAs generate undirected functional connectivity maps by using an exploratory approach to identify brain regions related to a researcher-specified seed region. PPIs extend SCAs to include task-related information by exploring how brain regions are related to a seed region (physiological condition) in the presence of a task (psychological condition). DCMs differ from SCAs and PPIs because they estimate effective connectivity maps by

projecting a task signal through the brain with a forward model. The maps include the driving and modulatory effects of the task, but they are typically fit and compared in a confirmatory way.

This work continued with a presentation of a connectivity method that is relatively new to adolescent brain research, but not to neuroscience generally: extended unified structural equation models (euSEMs) implemented in group iterative multiple model estimation (GIMME). This introduction was motivated by some of the limitations of SCAs, PPIs, and DCMs. Even though these approaches have yielded noteworthy insights into adolescent functional neural networks (Cho et al., 2013; Davidow et al., 2016; Hare et al., 2008; Somerville et al., 2011), they are not ideal for all research questions; no method is. For example, euSEMs implemented in GIMME permit exploratory identification of task effects in heterogeneous samples. They construct person-specific data-driven networks of time-indexed connections among ROIs. These directed functional connectivity maps contain contemporaneous and lagged connections among ROIs at the group- and individual-levels as well as driving and modulating task effects.

The unique features of euSEMs implemented in GIMME make it particularly attractive for applications to adolescent neuroscience. They produce person-specific networks that accurately reflect individual differences in brain development, while simultaneously informing normative development. It is not unreasonable to think that these person-specific results might have downstream relevance for individualized prevention and intervention efforts, a goal of developmental and clinical science (Beltz, Wright, Sprague, & Molenaar, 2016; Insel, 2014). For example, simulated shifts in network characteristics from middle to late adolescence might mark a decreased likelihood for risk-taking that could be developed without exposure to affectively arousing situations. Moreover, the transition into early adolescent network characteristics might mark the onset of functional reorganization, and thus, an optimal time for intervention.

euSEMs implemented in GIMME also identify directionality in ROI connections in the observed BOLD signal without making assumptions about neurobiology. Theoretical models in adolescent brain research, including the dual systems model, make predictions about the direction of connections, and GIMME can discern, for instance, whether activity in the NAcc predicts activity in the insula or whether activity in the insula predicts activity in the NAcc (see Figure 3 and Cho et al., 2013). Although this discernment can be statistically challenging, there are variations to GIMME that explicitly address this. For example, the GIMME-MS program

generates multiple, data-driven solutions when there is uncertainty about direction of prediction, and then a decision schema is used to determine the optimal solution (Beltz et al., 2016).

It is important to emphasize that the connectivity methods presented here are simply different. There is no quantitative silver bullet, and results of simulations comparing the methods would likely depend upon assumptions made when simulating the data. The ultimate way to match theory and methods in adolescent brain research is to identify the connectivity approach that is best suited to a particular research question, remembering that approaches can be complementary. For instance, both SCAs and PPIs are good for research questions related to network discovery because they require little theoretical input (only the specification of a seed region). SCAs are then optimal for resting state data, and PPIs for task-based data, especially block designs. DCMs are ideal for confirmatory research on the neural sequelae of task effects occurring at the millisecond (i.e., synaptic) level. Learning paradigms are particularly amendable to this approach (Stephan et al., 2010), as are paradigms based on biophysical causality. euSEMs implemented in GIMME are advantageous for research with heterogeneous samples (which dominate developmental neuroscience), and for research questions concerning connectivity in a known network; they require the specification of ROIs (more theoretical input than PPIs), but they generate the connections in a data-driven way (less theoretical input than DCMs).

It is also important to note that the conclusions of this work are not just applicable to SCAs, PPIs, DCMs, euSEMs, and to the dual systems model. Space did not permit consideration of all brain networks implicated in adolescent development (e.g., triadic model, Ernst, Pine, & Hardin, 2006; for others, see Blakemore, 2008; Fair et al., 2009; Nelson, Leibenluft, McClure, & Pine, 2005) or of all connectivity methods used in adolescent research (e.g., machine learning, Dosenbach et al., 2010; Granger causality, Hwang, Velanova, & Luna, 2010; for others, see Shaw, Grosbras, Leonard, Pike, & Paus, 2011; Stevens, 2016), but the general message about traversing the theory-methods divide generalizes to those theories and methods, too.

Increased understanding of adolescent brain function relies on theory and methods. When theories concern neural networks, empirical investigations must employ connectivity methods in order to test hypotheses. Otherwise, theory and methods will progress independently, and their impact will be limited. Just as neural networks provide an integrated picture of the brain, together theory and methods can provide an integrated picture of adolescence. Through this

integration, studies of adolescent brain connectivity may one day inform personalized prevention and intervention efforts that leverage resilience and limit risk.

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Footnotes

¹ Traditional PPI analysis concerns psychological conditions with two levels, but generalized PPI analysis concerns psychological conditions with three or more levels (for details, see McLaren, Ries, Xu, & Johnson, 2012).

² There are other variations of DCM, such as stochastic DCM, that do not require task input or confirmatory modeling. The stochastic model was developed for endogenous brain activity and can be applied to resting state data in an exploratory fashion (Friston, Li, Daunizeau, & Stephan, 2011). But, most work on this has been theoretical, and empirical applications have been simplistic and outside of the adolescent neuroscience literature.

³ Although it is possible to fit DCMs at the individual-level (see e.g., Stephan et al., 2010), this is uncommon in the literature, especially in adolescent brain research.

⁴ euSEMs can also be implemented in a confirmatory fashion in GIMME.

⁵ Vector autoregressive models, such as those used in Granger causality testing (Granger, 1969), have been employed in adolescent brain research (e.g., Hwang, Hallquist, & Luna, 2012). GCAs combine the time-indexed nature of BOLD fMRI data with the rationale that causes temporally precede effects to identify lagged connections and Granger causes in networks. For instance, ROI A is a Granger cause of ROI B if ROI A at t predicts ROI B at $t + 1$ above and beyond the degree to which ROI B predicts itself.

⁶ Additional versions of the program (as described in Beltz & Gates, under review) are also available from the author.

⁷ GIMME can also be implemented without task vectors, in which case unified structural equation models (uSEMs) are estimated (Gates et al., 2010). Thus, GIMME is well-suited for block, event-related, and resting state fMRI data (e.g., Beltz & Molenaar, 2015).

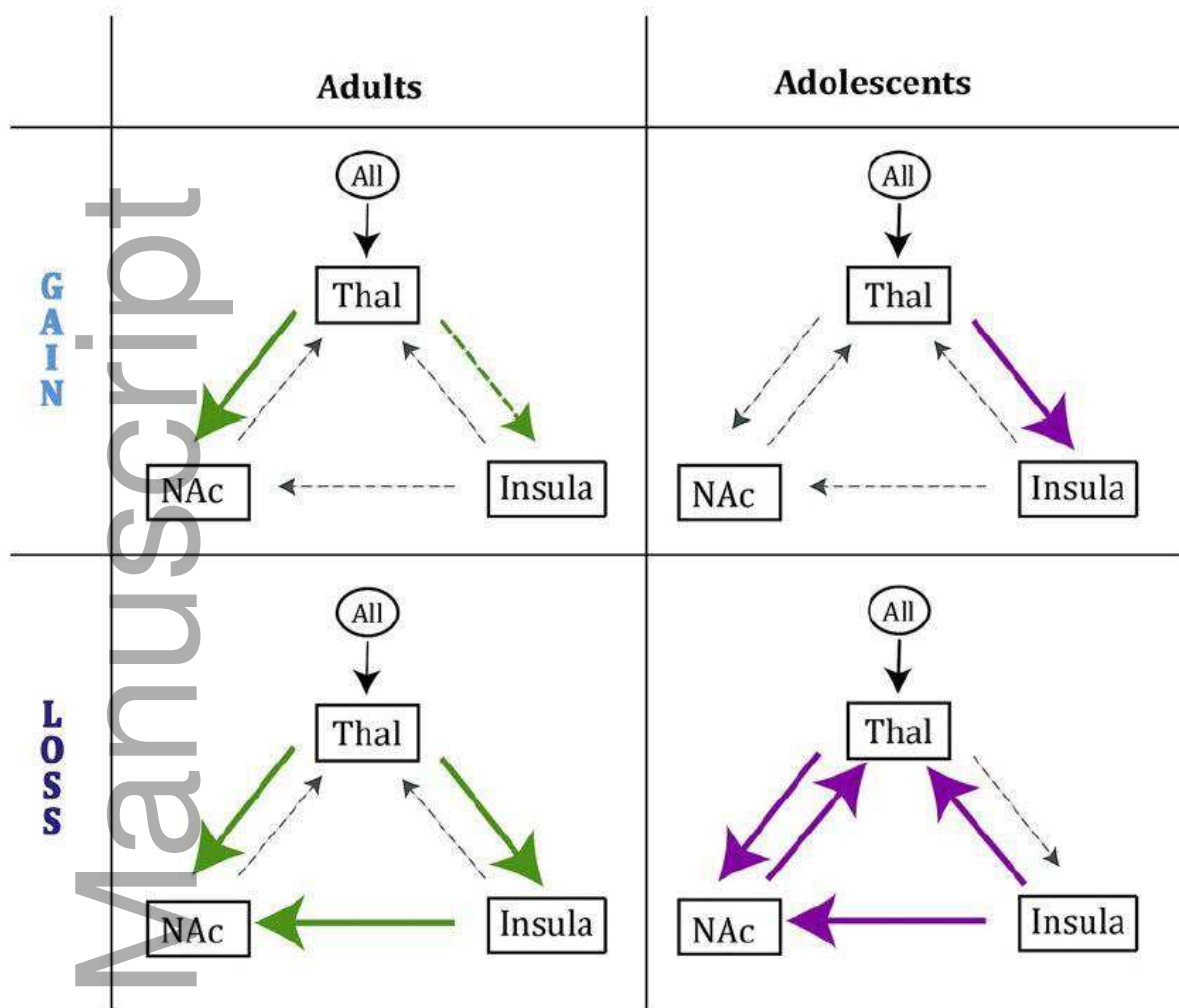


Figure 1. Modulatory DCM results from adolescents and adults completing a monetary incentive delay task, gaining money in some trials and losing money in others (Cho et al., 2013). The task condition has direct effects on the thalamus, and the dashed and colored arrows show the effects of the task on ROI connections. Dashed lines reflect non-significant modulation by the task condition; bold, colored arrows reflect significant modulation by the task condition; dashed, colored arrows reflect a trend. Although the modulatory effects significantly differed from zero, they did not significantly differ across conditions or groups. (Reproduced with permission from Elsevier from Cho et al., 2013.)

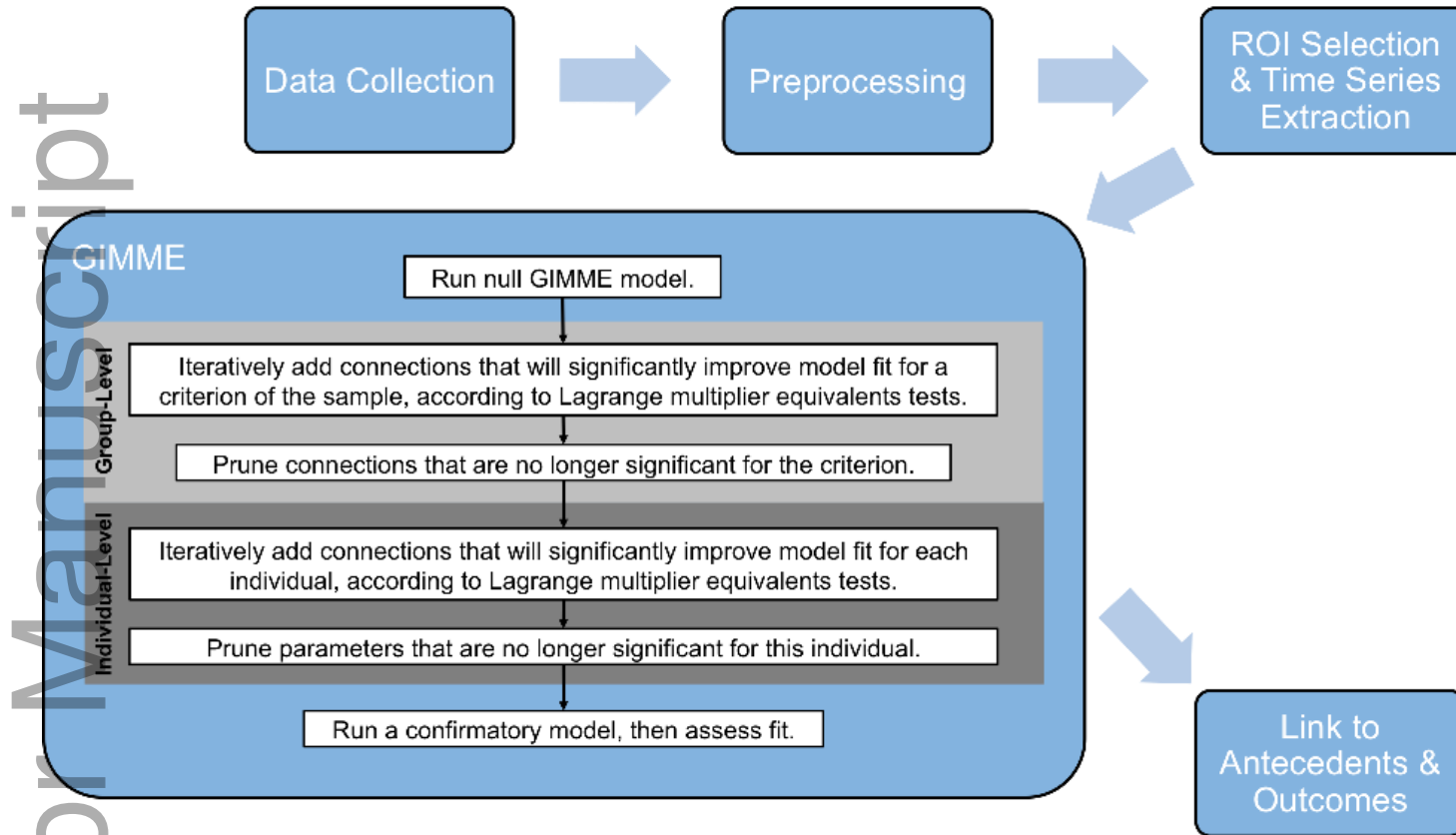
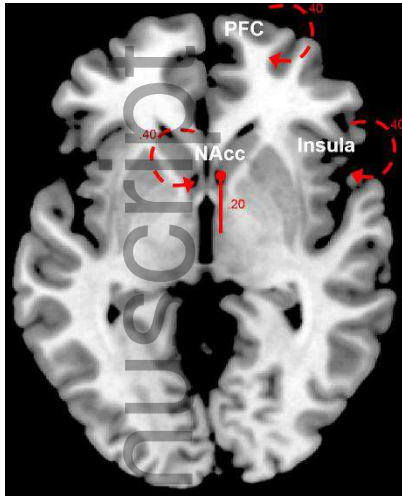
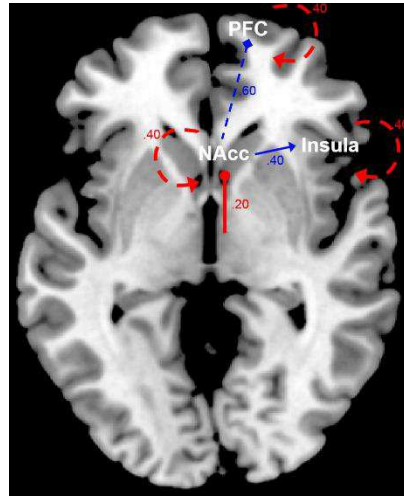


Figure 2. A flow chart showing: (in blue): the general steps of a GIMME analysis from data collection all the way through the relation of network results to psychological antecedents and outcomes; and (in gray): the specific steps used by GIMME to implement (extended) unified structural equation models to create data-driven, person-specific networks that contain group- and individual-level connections. (Obtaining permission to reproduce a modified version of the GIMME analysis step from Beltz & Gates, under review.)

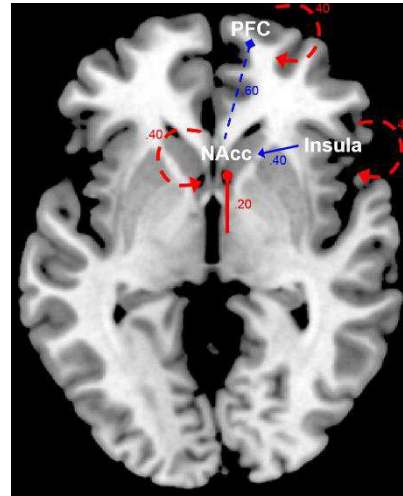
A. Group-level simulation



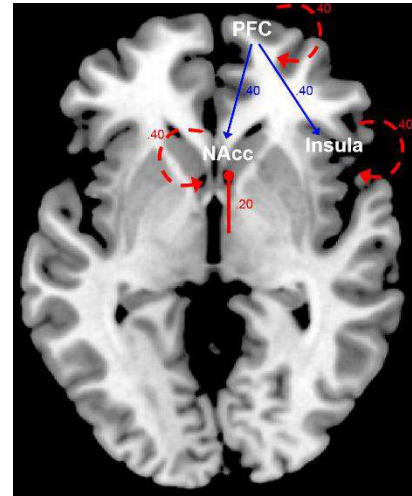
B. Early adolescent simulation



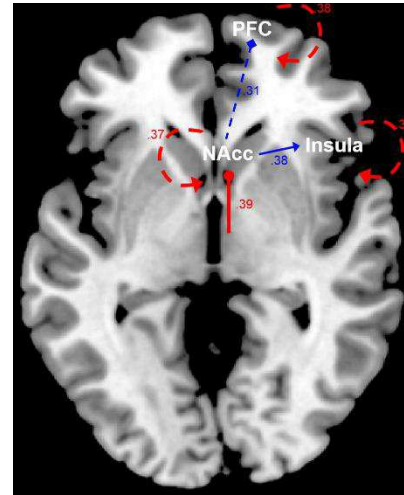
C. Middle adolescent simulation



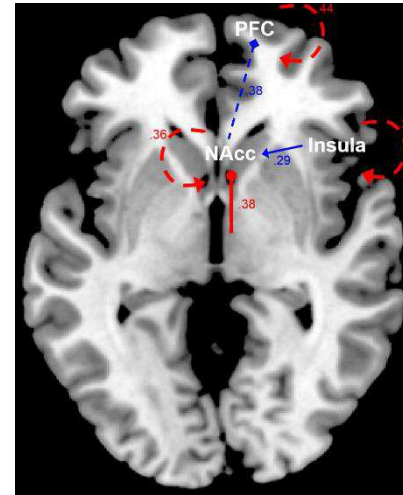
D. Late adolescent simulation



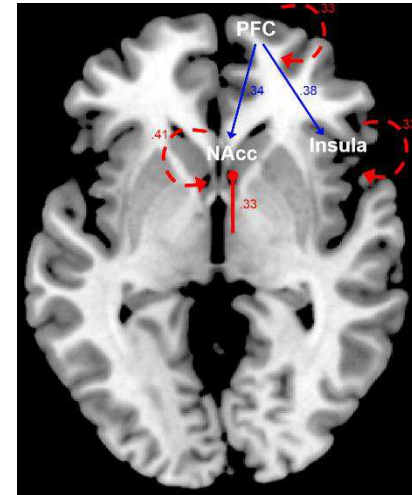
E. Early adolescent result



F. Middle adolescent result



G. Late adolescent result



- ← - - - lagged group connection
- - - - contemporaneous group direct task effect
- ← - - - contemporaneous individual connection
- ◆ - - - lagged individual modulating task connection

Figure 3. Simulation details and results for an euSEM analysis implemented in GIMME. Networks show directed functional connectivity maps underlying adolescent responses to monetary gains. Networks are overlaid on a standard space axial brain slice (in neurological orientation at $z = -2$). Blue lines reflect group-level network features present in all maps; red lines reflect individual-level network features present in one or more maps; solid lines reflect contemporaneous connections; dashed lines reflect lagged connections; arrows reflect ROI connections; circles reflect driving task effects on ROIs; diamonds reflect modulatory task effects on ROI connections. All network features have magnitudes (standardized β weights) associated with them. A.) The group-level network simulated for all adolescents ($N = 30$). B.) A network simulated to reflect early adolescent responses to monetary gains ($n = 10$), with bottom-up connectivity. C.) A network simulated to reflect middle adolescent responses to monetary gains ($n = 10$), with features of bottom-up and top-down connectivity. D.) A network simulated to reflect late adolescent responses to monetary gains ($n = 10$), with top-down connectivity. E.) Resulting representative network for an early adolescent that fit the data well: $\chi^2(21) = 25.72$, $p = .22$, CFI = .99, NNFI = .99, RMSEA = .03, SRMR = .03. F.) Resulting representative network for a middle adolescent that fit the data well: $\chi^2(21) = 28.03$, $p = .14$, CFI = .99, NNFI = .98, RMSEA = .04, SRMR = .03. G.) Resulting representative network for a late adolescent that fit the data well: $\chi^2(21) = 25.72$, $p = .22$, CFI = .99, NNFI = .98, RMSEA = .03, SRMR = .03. PFC: prefrontal cortex; NAcc: nucleus accumbens.