Systematic review and meta-analysis of socio-cognitive and socio-affective processes association with adolescent substance use.

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Abstract

Background. Social impairments are important features of a substance use disorder diagnosis; and recent models suggest early impairments in socio-cognitive and -affective processes may predict future use. However, no systematic reviews are available on this topic. **Methods**: We conducted a systematic review and meta-analyses exploring the association between social- cognitive and -affective processes (empathy, callous-unemotional (CU) traits, theory of mind, and social cognition) and substance use frequency (alcohol, cannabis, general drug use). We examined moderating effects of study design, gender, age, and weather conduct problems were controlled for. We also review brain studies related to social cognition and substance use disorder (SUD) risk. **Results**: Systematic review suggested a negative association for positively valenced constructs with substance use but mixed results on the negatively valenced construct CU traits. Meta-analyses revealed moderate positive association between CU traits with alcohol and general drug use but no significance with cannabis use. Moderate effect sizes were found for CU traits in youth predicting severity of substance use by late adolescence and significantly accounted for variance independently of conduct problems. Significant moderators included gender proportions, sample type, and age. Neuroimaging meta-analysis indicated 10 coordinates that were different in youth at a high risk/with SUD compared to controls. Three of these coordinates associate with theory of mind and social cognition. **Conclusion**: Socio-cognitive and -affective constructs demonstrate an association with current and future substance use, and neural differences are present when performing social cognitive tasks in regions with strongest associations with theory of mind and social cognition.

Key words: adolescents, substance use, risk, empathy, callous-unemotional traits, theory of mind, social cognition

Substance use commonly increases during early adolescence, around 13 years old, and peaks in late adolescence, around 18-19 years of age (Dennis & Scott, 2007; Rutherford et al., 2010). These normative age patterns of use see a steady decline into adulthood; however, a subset persist in their use, with some developing a substance use disorder (SUD). There are many preadolescent phenotypes known to increase risk of SUD such as reward sensitivity, poor impulse control, and behavioral disorders (Argyriou et al., 2018; Ryan et al., 2013; Verdejo-García et al., 2008; Volkow et al., 2010). Identification of such risk factors help in prediction of SUD. However, there is one commonly overlooked phenotype – social functioning and its underlying factors.

Problems of social functioning and bonding have been well described in youth with persistent substance use and these problems are traditionally considered to result from substance use. For example, social impairment is one of four diagnostic domains of SUD involving strained and problematic interpersonal relationships as well as giving up major roles and social activities in order to use substances (American Psychiatric Association, 2013). However, recent models and preliminary evidence suggest factors underlying impaired social functioning and bonding (e.g. social cognition, empathy, theory of mind) may predispose to persistent substance use and SUD. Massey et al. (2017) propose that impairments in empathy (i.e. the ability to understand others thoughts and share their feelings) are an early SUD risk factor; in this model, those with social impairments are more likely to persist in substance use despite substance related social consequences. Additionally, prevention programs target social competence/skills as a means to reduce substance use (Das et al., 2016), further suggesting that social domains may lead into substance use and improving social skills may reduce future substance use risk.

Though potentially important to our understanding of addiction, behavioral and neural models of socio-cognitive and -affective processes are not well defined in models on substance use and addiction. For example, Volkow and colleagues (Volkow et al., 2016) emphasize social skills development and assessing social rewards for individuals SUD prevention and recovery. However, Volkow and colleagues' biological model does not include socio-cognitive and -affective processes. Identifying whether reliable evidence exists on these associations can improve existing models by either including or excluding relevant socio- cognitive or -affective factors. It is plausible that excessive substance use disrupts factors underlying social bonding, and that impairments in factors underlying social bonding increases potential for substance use and later SUD (Young et

al., 2011) – highlighting the need to elucidate social processes underlying social impairments both behaviorally and neurally as a phenotypic risk factor.

1.2 Socio-Cognitive and -Affective Factors Examined in this Review

1.2.1 Empathy

Empathy is generally agreed in the literature to involve both socio-cognitive and -affective components (Decety, 2010; Shamay-Tsoory et al., 2009). *Cognitive empathy* involves the ability to take on and understand others perspective, whereas *Affective empathy* involves sharing another's emotional experience (Decety, 2011; Decety & Cowell, 2015). Neuroimaging meta-analyses distinguish these processes neurally, suggesting that cognitive processes involve the medial prefrontal cortex, temporoparietal junction, and the posterior cingulate cortex (constituting the default mode network). On the other hand, affective processes involve the anterior insula and anterior cingulate cortex (constituting the salience network) (Decety & Lamm, 2007; Eres et al., 2015; Fan et al., 2011; Lamm et al., 2011).

1.2.2 Callous-Unemotional Traits

Callous-Unemotional (CU) traits involve affective impairments including a lack empathy, remorse, and guilt (Frick & White, 2008) that are broader than, but include primary impairments of socio- affective processes (Jones et al., 2010; Schwenck et al., 2012; Winter et al., 2017). Behaviorally, those with CU traits are characterized by antisocial behavior such as persistent disregard for others, uncaring behavior, and the use of others for their own gain (Blair et al., 2014). Those with higher CU traits show less neural activity and aberrant connectivity patterns in default mode and salience networks (Pu et al., 2017; Umbach et al., 2017; Yoder et al., 2016).

1.2.3 Theory of Mind

Theory of mind is a socio-cognitive process referring to the ability to infer and attribute mental states to others and reason about the thoughts, beliefs, and emotions of others (Frith & Frith, 2005; Mitchell, 2005). Like other socio-cognitive processes, neural underpinnings of theory of mind primarily involve the default mode network (Li et al., 2014).

1.2.4 Social Cognition

Social cognition involves both social-cognitive and -affective processes that broadly refer to processes that interact with the social environment, including responding to social stimuli and making social decisions (Frith, 2008). This broad construct could subsume theory of mind and empathy with impairments at least partially involved in CU traits. Neural underpinnings of social cognition include the default mode and salience networks (Adolphs, 2009; Frith, 2007).

1.3 Neural Underpinnings of Addiction

Volkow et al. (2016) demonstrate those with addiction have neuroimaging findings that differ from typically developing brains overlapping brain regions underlying socio-cognitive and -affective processes. This includes the default mode, which in addiction is involved in preoccupation and anticipation of substance use, as well as the salience network which, in addiction, is involved in withdrawal and negative affect (Volkow et al., 2016). Beyond neural regions underlying social processes, the ventral striatum and global pallidus show aberrant functioning, which are involved in addictive processes of reward in response to substances during binging and intoxication. Even though brain differences beyond social processes are demonstrated, it is unknown if the overlapping brain regions between addiction and both socio-cognitive and -affective processes account for any predisposed vulnerability to persistent substance use.

1.4. Current Study

The present study examines the association between socio-cognitive and -affective processes with substance use and future substance use severity. It is plausible that deficits in socio-affective processes may attenuate the response to substance use-related consequences (Massey et al., 2017) and deficits in socio-cognitive processes may diminish perception of social connectedness (Galinsky et al., 2005; McWhirter et al., 2002; Wang et al., 2014) and/or engagement in prosocial behaviors (Fett et al., 2014; Imuta et al., 2016; Tamnes et al., 2018), leading individuals to prefer substances over social connection.

Here we aim to qualitatively synthesize and quantitatively examine available evidence on the association between socio-cognitive and -affective functioning in adolescents in relation to substance use and predictions of future use. Because social processes and substance use show gender-related differences (Brady & Randall, 1999; Christov-Moore et al., 2014; Geary, 2002; Russell et al., 2007; Stickle et al., 2012) that may also vary by sample type (clinical versus community; Colins et al., 2020; Cotter et al., 2018; Decety & Moriguchi, 2007; Herpers et al., 2016; Loney et al., 2003), we explore gender and sample effects. Age is also explored as a moderator because normative use patterns change with age (Dennis & Scott, 2007; Rutherford et al., 2010). In addition to the behavioral evidence we review relevant neural evidence of SUD risk.

We hypothesize that both socio-cognitive and -affective constructs will associate with concurrent substance use (e.g. cannabis and alcohol consumption) and predict severity of substance use (i.e. higher frequency) longitudinally. Specifically, positively valenced constructs (empathy, theory of mind, social cognition) will negatively associate, whereas negatively valenced construct (CU traits) will positively associate, with substance use, respectively. For moderation, we expected forensic and clinical samples to have lower ratings on socio-cognitive and -affective processes and higher rates of substance use in comparison to community samples. Because substance use and impairments in socio-cognitive and -affective processes underlie internalizing and externalizing behavioral issues (Bornstein et al., 2010; Gambin & Sharp, 2016) that are commonly present in those with a SUD (Colder et al., 2018; Currie et al., 2005; Jun et al., 2015), we expect studies controlling for conduct problems to have a weaker effect than those that do not account for this variance in the analysis. Additionally, we examine the effects of age and gender, but, because of the sparse literature, we made no directional hypotheses on these as moderators. The present study addresses a critical need by examining constructs underlying both cognitive and affective social processes in relation to substance use severity, as well as the underlying neural mechanisms, associated with concurrent use and prediction of future use severity.

2. Methods

Prior to the beginning of the study, the study protocol was registered (PROSPERO 2019 CRD42019124948). A four-step process then was implemented to select the studies to be included in the review in accordance with PRISMA guidelines (Moher et al., 2009). First, studies relevant to this review were identified

through literature searches using PubMed, PsychINFO, and Web of Science. Searches consisted of keyword combinations of the terms (1) socio-cognitive and -affective processes (i.e. empathy, theory of mind, social cognition, and CU traits) and (2) substance use including specific substances (Supplemental Table 1). *PubMed's* medical subject headings search and both *PsychINFO* and *Web of Science* term search guided search term selection. A forward and backward search using the identified articles was completed to locate additional articles.

2.1 Inclusion and Exclusion Criteria

We included studies if they (1) were empirical studies reporting on the association between socio-cognitive or -affective processes associating with substance use or SUD risk; (2) had substance use, addiction, SUD, or SUD risk as an outcome (via self-report, laboratory, or neurobiological measures); (3) used a sample that had a mean age ≤ 18, (4) used quantitative methods; and (5) published in English. Studies using measures of psychopathic traits in adolescents had to report on a subscale or measure assessing CU traits to be included. Additionally, we excluded studies with measures of emotional intelligence because the broadness of the construct is outside the aims of the present study.

2.2 Bias Assessment

Four reviewers independently assessed each included article using a modified version of the Cochrane bias assessment scale (Higgins et al., 2011). Reviewers discussed applicability of the article to the research question and came to consensus about inclusion and bias ratings. Because the current review of studies were all observational, a risk of bias was assessed as high, low, or unclear for the six domains: selection, measurement (e.g. reliability coefficients >.70), detection bias (appropriate measurement for construct studied), differential attrition, incomplete data, and selective reporting. Our qualitative synthesis focused on low-risk studies, defined as studies with low risk on most (4 out of 6) domains assessed. Medium risk studies were those that had high risk of bias on one domain or unclear risk of bias on most (4 out of 6). Studies deemed to be a high risk were those agreed to have a high risk of bias on more than one domain.

2.3 Data Extraction and Synthesis

All four authors extracted data and methods from the included studies using a custom-made table (Table 1 [behavioral], Table 2 [imaging]). Data abstraction included study samples (e.g. sample type, size, groupings,

diagnostic groups studied), key methods used (study design and type, measures used, analysis methods), and summary of the results (direction, strength, and significance of the relationship between empathy and substance use and risk outcomes). The strengths of association were assessed looking at the direction and magnitude of the association as well as the statistical significance.

2.4 Selection of Studies for Meta-Analysis

Studies included in the systematic review were screened by all authors for appropriateness for meta-analysis. Any disagreements about appropriateness for meta-analysis were resolved by first and second authors. Considerations included comparison of measures, study design, and number of studies available. For behavioral meta-analysis, we were only able to analyze CU traits studies due to the limited number of studies and lack of comparable outcome variables for other measures of social cognition. Inclusion for behavioral meta-analysis included a self-report measure for CU traits and substance use frequency measure. If male and female were reported separately, we treated each as a point estimate for an independent population for boys and girls. For the neuroimaging meta-analysis, we included studies if they performed a social task that compared blood oxygen level dependent (BOLD) responses between groups of youth who were deemed as a high risk for or current SUD with typically developing controls.

2.5 Behavioral Meta-Analytic Strategy

Effect sizes for analysis were converted to Hedge's g for comparison using the "esc" package and, where necessary, we calculated standard error using the "dmeter" package (Harrer et al., 2019; Lüdecke, 2019). We conducted all analyses using the "metaphor" package for R version 4.0.2 (R Core Team, 2020; Viechtbauer, 2010). A priori, we expected studies were unlikely to be identical. We tested heterogeneity of the studies and if the test was insignificant, we compared random and fixed effect model results for comparison. If identical we reported the random-effects model. For cross-sectional studies we conducted separate meta-analyses by substance use outcome (i.e., alcohol, cannabis, general drugs). When included studies for an analysis included both between- and within- subject design, we accounted for potential differences by including study design as a moderator.

For longitudinal studies, we ran analyses on a general drug use frequency measure. An important consideration for this meta-analysis was controlling for effects of conduct problems. Where available, we

calculated effect sizes for longitudinal analyses that controlled for conduct problems. We accounted for studies that did not control for conduct disorder in mediation. Most articles examined a baseline measure of CU traits predicting later substance use; thus we calculated effect sizes that assessed a constant CU trait over time predicting substance use when growth factors may have also been available (i.e. intercept betas in growth models used for effect sizes).

To statistically assess publication bias, we used a multifaceted approach including 1) a visual inspection of a funnel plot, 2) examined weighted regressions of funnel plot asymmetry using standard error, and 3) compared a trim-and-fill model using a L0 estimator. Using this approach, we would determine there is systematic bias if 1) there is considerable asymmetry in the funnel plot, 2) the regression required a significant statistic, and/or 3) trim-and-fill models substantively different than the model tested. If we determined there was bias and the trim-and-fill model corrected for this bias, then we report on the trim-and-fill model. We confirmed effect sizes by simulating 5,000 studies using the metaphor package simulate function. Simulated effect sizes within five-hundredths of a point from the original are considered confirmed.

After assessing the properties of the unconditional models, we explored moderation of the association between CU traits and substance use. Where relevant for all studies, we tested moderation for age, proportion of males in the sample, design (within or between subject), sample type (community or forensic/clinical), and whether they controlled for conduct disorder. For longitudinal studies, additional moderators were tested for time points, lag in time between each time point, and the interaction between them. To decrease Type I error inflation, we used Knapp and Hartung's adjustment for the moderators significance (Viechtbauer, 2010).

2.6 Neuroimaging Studies Meta-Analytic Strategy

Neuroimaging meta-analyses were conducted on studies that provided coordinates with a social task comparing higher risk versus control participants. We conducted the neuroimaging meta-analysis using the activation likelihood estimation technique implemented in GingerALE (Turkeltaub et al., 2002; www.brainmap.org/ale/) using MNI152 coordinates. The likelihood of neural differences between groups who were categorized as a higher risk (externalizing symptoms and family history or higher instances of use and CU

traits) and controls were estimated on contrasts reported in primary studies. Clusters forming thresholds included a false discovery rate (FDR) corrected p value at < 0.01 and a minimum volume of 500mm. We calculated the centroid of clusters identified in the analysis and compared with independent meta-analytic locations from the Neurosynth database (Yarkoni et al., 2009; www.neurosynth.org). From Neurosynth we examined associations of the coordinates identified ALE maps with social constructs (i.e. empathy, theory of mind, social cognition) as well as addiction to indicate if identified regions associated with similar findings across studies.

3. Results

3.1 Study characteristics

We identified 32 articles (Supplemental Figure 1) that were included in the systematic review (29 [88%] behavioral and four [12%] neuroimaging; Figure 1). Social constructs represented included: five empathy studies (15%), 21 CU trait studies (63%), two theory of mind studies (6%), and six social cognition studies (18%). Twelve (36%) were longitudinal studies and 22 (66%) were cross sectional studies. Out of the 21 CU trait studies, the meta-analysis consisted of six) cross-sectional studies (29% of CU studies) and seven for longitudinal studies (33% of CU studies) with a total of 21 relevant effect sizes. Three neuroimaging studies (75% of neuroimaging studies) were included in the neuroimaging meta-analysis. Behavioral study samples ranged from 63 to 3,436 participants, whereas neuroimaging study samples ranged from 16 to 78 participants. The mean age across studies was 14.92 (range= 11.5-18). The average proportion of males across studies is 65% (range 0-100%).

3.2 Risk of Bias Assessment

Of the 32 articles included, all authors agreed that 24 had a low risk of bias (73%), seven (22%) with medium risk, and two (6%) with high risk (Supplemental Table 2; Supplemental Figure 2). Amongst the medium risk studies, two had high risk for incomplete outcome data, one for selection bias, and one for measurement bias while the rest had more unclear ratings than low. High risk studies had high bias in more than one category including outcome data, detection, selective reporting, and measurement bias. The majority of unclear ratings occurred for selection (12) and incomplete data (11) bias. Overall, most studies were rated favorably with a low

risk of bias indicating high quality evidence. Of the studies meeting inclusion criteria in the meta-analysis, except one medium bias study, all were rated a low bias.

3.3 Systematic review synthesis

3.3.1 Empathy

Five studies were found on the association between empathy and substance use including one longitudinal study (20%) and four cross-sectional designs (80%). Of these studies, two focused on general empathy (40%) whereas three differentiated between cognitive and affective processes (60%) (Table 1). The quality of evidence suggested only one study had a high risk of bias due to measurement and selective reporting bias whereas the other four studies had low risk of bias (Figure 2). Findings in this section did not appear to be due to individual study bias.

Associations between empathy and substance use. Overall, cross-sectional findings suggest that general, as well as both cognitive and affective empathy, negatively associate with concurrent substance use (Anh et al., 2011; Ferreira et al., 2012; Laghi et al., 2019; Luengo et al., 1994) (Table 1). Of importance, two studies suggested an indirect effect via drug refusal efficacy – one study on general empathy and another on cognitive empathy (Anh et al., 2011; Laghi et al., 2019). Although all correlations showed negative associations, regressions of cross-sectional data controlling for covariates showed mixed results for the association between affective empathy and substance use. However, longitudinal findings found that increases in affective empathy over time predicted decreases in substance use (Winters et al., 2020).

Influences on relationship between empathy and substance use. There was little evidence for other influences on the above associations. Other than one study finding general empathy did not moderate the association between gender and substance use (Anh et al., 2011), gender differences were not well examined in the available literature. We were unable to examine differences in community and clinical samples, whether behavioral issues accounted for differences, or effects of age from the available literature. Additionally, no neural studies were available in the present search. It is unclear if biological processes beyond subjective report may account for cognitive and affective empathy when associating with substance use. Moreover, future longitudinal

studies could help untangle socio-cognitive processes relationship to substance by testing the moderating effect of drug refusal-efficacy.

3.3.2 Callous-Unemotional Traits

We included 21 studies focusing on CU traits. Ten of these studies were cross-sectional (50%), nine were longitudinal (45%), and one was retrospective (5%). Eight of these studies were of community samples and 12 sampled from forensic or clinical samples (Table 1). Risk of bias consensus suggested five articles (25%) had a medium risk of bias with the greatest bias in measurement and incomplete outcome data bias. Fifteen articles (75%) had low risk of bias (Figure 2). Studies risk of bias (between medium and low risk) did not change the pattern of findings across studies.

Associations between CU traits and substance use. Overall findings on this association were mixed. Five cross-sectional studies (Pedro Pechorro et al., 2016; Pechorro, da Silva, et al., 2017; Pechorro, Gonçalves, et al., 2017; Pechorro, Hawes, et al., 2017; P. Pechorro et al., 2016) and three longitudinal studies (Andershed et al., 2018; Thornton et al., 2019; Wymbs et al., 2012) showed positive correlations (no controls) with substance use, which is supported in group comparison studies (Chabrol et al., 2012; Ray et al., 2016). Regarding conduct problems, two cross-sectional studies (Cecil et al., 2017; Euler et al., 2015) and two longitudinal studies (Andershed et al., 2018; Wymbs et al., 2012) found conduct with CU traits accounted for more variance in substance use. Two studies found CU traits associated with slight decreases in substance use over time (Fanti, 2013; Wymbs et al., 2012). However, four longitudinal studies (Anderson et al., 2018; Baskin-Sommers et al., 2015a; Muratori et al., 2016; Waller et al., 2018) found that after accounting for conduct problems (either continuously or group separation) that consistency and/or growth in CU traits accounted for unique variance when predicting increases in substance use over time. Moreover, one study found CU traits moderated the relationship between conduct problems and substance use (Wymbs et al., 2012), whereas another found CU traits in addition to preexisting impulsivity accounted for increases in future substance use (Dubas et al., 2017).

Gender influence on CU traits and substance use. Gender related findings were also mixed. Five cross-sectional studies (Pedro Pechorro et al., 2016; Pechorro, da Silva, et al., 2017; Pechorro, Gonçalves, et al., 2017;

Pechorro, Hawes, et al., 2017; P. Pechorro et al., 2016) and two longitudinal studies (Andershed et al., 2018; Thornton et al., 2019) demonstrated positive associations for both males and females. However, one longitudinal study found within females there was no significant association between baseline CU traits and substance use, and CU traits protected females from later substance use (Wymbs et al., 2012).

Sample influence on CU traits and substance use. The pattern of findings did not appear to be different in samples of community versus forensic samples.

Neuroimaging findings on CU traits and substance use. Neuroimaging findings consisted of one study (Sakai et al., 2017) that concurrently compared adolescent controls with those with conduct issues and those with conduct issues with high CU traits on a prosocial giving game that was played in an fMRI machine (Table 2). Those who were high in CU traits had more substance use or dependence and less cognitive and affective empathy than conduct problems alone or controls. Sakai and colleagues found a negative mean activation in a right insula cluster (right insula, inferior frontal gyrus, and superior temporal gyrus) in those with CU traits that was not present in the other two groups. CU traits positively associated with the left inferior parietal lobule and left posterior cingulate cortex.

3.3.3 Theory of Mind and Social Cognition

We found only one study examining theory of mind and substance use (Table 1). That study had a medium risk of bias (Figure 2). We found 5 studies of social cognition: two behavioral longitudinal studies (40%) and three neuroimaging studies (60%) (Table 1). One study had a high level of bias for detection and incomplete outcome bias, and the other four studies had low bias risk (Figure 2). The high risk study on one parameter appeared to diverge from the consistency of the other results, which is discussed below.

Theory of mind associating with substance use. When examining both cognitive and affective theory of mind, the only significant finding was the second order affective theory of mind (i.e. the ability to predict what one person thinks a different person thinks and feels). Interestingly, cognitive, and affective empathy did not have a significant association, yet the theory of mind finding held.

Social cognition associating with substance use. Longitudinal studies agreed that social cognition (social reciprocity, level of social cognitive distortions) temporally associated with substance use in adolescents. One study found that higher risk for SUD predicted social cognitive distortions at 12-14 predicted marijuana use prodromal to SUD at 19 (Kirisci et al., 2004). Fluharty and colleagues (Fluharty et al., 2018) report similar findings from retrospective reports but not in prospective longitudinally collected data, though this study was rated as a high risk of bias. In addition, the social cognition variable assessed by Fluharty and colleagues (poor non-verbal communication at age 8 as a measure of social cognition) may better map on to developmental delays and not the socio-cognitive processes of interest here. We could not determine the effects of gender, sample, or conduct issues on these relationships. The findings generally support that social cognition is negatively associated with substance use.

Neuroimaging findings on social cognition and SUD risk. Neuroimaging findings converge on the frontal cortex and amygdala across studies (Table 2). During facial recognition tasks, adolescents identified as a higher risk for SUD (family history of substance use and externalizing symptoms) showed higher activity in medial frontal and orbital regions both when looking at angry (Hulvershorn et al., 2013) and happy faces (Cservenka et al., 2014). During resting state, functional connectivity of the amygdala with the rest of the cortex was different in youth at high SUD risk when compared to controls (Cservenka et al., 2014). A brain volume study supported that a lower ratio of amygdala to orbital frontal cortex volume in adolescence predicted onset of SUD by late adolescence/early adulthood (O'Brien & Hill, 2017). Together these studies suggest patterns of differences in the medial and orbital frontal regions as well as subcortical amygdala are present in youth at higher risk for SUD.

3.3.4 Summary of Systematic Review

The positively-valenced constructs examined here appear to be negatively associated with substance use. When considering empathy, the cognitive components appear to indirectly associate with greater efficacy in refusing substances, whereas affective components have a direct negative association with substance use. Neither theory of mind nor social cognition studies corroborated the substance refusal finding; however, social cognitive

errors longitudinally predicted substance use severity leading to SUD. Social reciprocity also retrospectively predicted odds of use. Gender and sample type (community vs. clinical) were not investigated in these studies. Both cognitive and affective components of social cognition appear to predict substance use but there is a clear need to further examine socio- cognitive processes in relation to drug refusal efficacy.

Amongst studies on the negatively valenced CU trait construct, the findings were mixed. A few studies showed a positive association, while others suggested that controlling for conduct disorder accounted for this association. Analyses examining the effects of sample type and gender were also mixed. Several studies showed an association between CU traits and both concurrent and future substance use. However, this systematic review could not determine if conduct disorder accounted for this association, or the magnitude of potential effects of sample type or gender. These inconsistencies are addressed by meta-analysis (below).

Systematic review of the available neuroimaging studies suggested that youth who at a higher risk for SUDshowed differences in medial frontal cortical regions (medial prefrontal cortex, orbital frontal cortex, medial orbital gyri, superior temporal gyri) and subcortical regions associated with emotional arousal (anterior insula and amygdala) when performing a social cognitive task. When performing a prosocial giving task, CU traits are associated with activation patterns in an insular cluster (right anterior insula, inferior frontal gyrus, and superior temporal gyrus) such that those with CU traits have a negative activation pattern whereas the other groups (conduct issues with low CU and controls) have a positive activation. Overall, it appears the insula, amygdala, and both medial and orbital frontal regions are important in socio-cognitive and -affective tasks in relation to risk for SUD.

3.4 Meta-analysis

3.4.1 Cross-Sectional Model of Alcohol

There were six separate effects included in the random effects model with concurrent alcohol use as the outcome (Table 3, Figure 1). The association between CU traits and alcohol use was moderate and positive (g= 0.32, p= 0.04, simulated g= 0.32). The Q-statistic suggested these studies were homogeneous (Q= 1.67, p= 0.89); however, examination of the fixed effects model revealed the same effect size as the random effect model. Visual

inspection of the funnel plot did not reveal an obvious asymmetry, and this was supported by an insignificant regression test (t= -0.19, p= 0.85). A trim-and fill model detected one absent effect that raised the effect size slightly (g= 0.38, p= 0.01). Given the other two bias checks did not suggest any issues, and interpretations were not changed by trim-and-fill model results, we decided to report on the original random effects model.

3.4.2 Cross-Sectional Model of Cannabis

There were four separate effects included in the random effects model for cross-sectional cannabis use (Table 3, Figure 1). The association between CU traits and cannabis use was moderate and positive but not significant (g = 0.31, p= 0.08, simulated g = 0.31). The Q-statistic suggested a homogenous sample (Q= 1.06, p= 0.79); however, examination of the fixed effects model revealed the same effect size as the random effect model. Visual inspection of the funnel plot did not reveal an obvious asymmetry, and this was supported by insignificant regression for asymmetry (t= 1.00, p= 0.32). A trim-and-fill model identified one absent effect that reduced the overall effect but did not change interpretation of results (g= 0.25, p= 0.12). Given the previous two checks were acceptable and there was no difference in interpretation, we report on the random effect model.

3.4.3 Cross-Sectional Model of Drugs

There were three separate effects included in the random effects model for cross-sectional drug use (Table 3, Figure 1). The positive association between CU traits and drug use was moderate (g= 0.56, $p < 0.0001$). The Q-statistic suggested a homogeneous sample (Q= 0.36, p= 0.84); however, examination of the fixed effects model revealed the same effect size as the random effect model. Visual inspection of the funnel plot revealed a potential asymmetry; however, there was an insignificant regression for asymmetry (t= -0.46, p= 0.65). A trim-and-fill model identified two absent effects (g= .58, $p < 0.0001$, simulated g = 0.58). Given we visually detected asymmetry and the trim-and-fill model detected two missing effects we report on the trim-and fill model – this did not change interpretation of the effect.

3.4.4 Longitudinal Model of Drugs

There were seven separate effects included in the random effects model for longitudinal drug use (Table 3, Figure 1). The association between CU trats and longitudinal drug use was moderate (g= 0.48, p < 0.001, simulated g= 0.48). Supporting the use of a random effects model, the Q-statistic was significant (Q= 24.69, p< 0.001). Visual inspection of the funnel plot did not reveal an obvious asymmetry, and this was supported by insignificant regression for asymmetry (t= 0.14, p= 0.88). A trim-and-fill model detected no missing effects.

3.5 Meta-Analysis Moderation Models

Despite four exceptions, moderation tests revealed little evidence of moderation (Table 4). Cross-sectional studies shown no moderating effects. Longitudinally, the association between CU traits and drug use was moderated by the proportion of males, with studies with a higher proportion of males showing a higher positive effect (Figure 2). The type of sample also moderated this association with forensic/clinical samples having a stronger positive effect (Figure 3). Age also moderated this association where higher longitudinal mean age collections shown stronger associations (Figure 4). In addition, we separately examined studies that did not control and did control for conduct problems. The studies that did not control for conduct problems had a stronger effect, but both study types had significant effects (Figure 3).

3.6 Neuroimaging Meta-Analysis

Analysis of neuroimaging data revealed statistically significant differences in 10 coordinates when comparing typically developing youth to those identified at a high risk (Table 5; Supplemental Figure 3). Consistent with the systematic review of neuroimaging studies, we see patterns of medial frontal regions, but little subcortical differences. We compared the coordinates identified in this meta-analysis with findings from the general literature, by searching those coordinates in Neurosynth. Three of the ten coordinates had significant associations with socio-cognitive and -affective processes (Figure 5); all other coordinates did not have significant findings with any terms on Neurosynth. The three coordinates that did associate had a low association with addiction and empathy and the highest associations (positive or negative) with social cognition and theory of mind. The angular gyrus and superior frontal medial gyrus had positive associations whereas the superior occipital

lobe had negative associations with social cognition. The superior frontal medial gyrus had the strongest association.

4. Discussion

The current review and meta-analysis represent a timely analysis of the literature on the association between socio-cognitive and -affective constructs with substance use. The literature for empathy and social cognition generally converge on a negative association with substance use. These studies did not capture gender differences, associations with age, or clinical samples. On the other hand, studies of CU traits produced several mixed findings on gender, impact of conduct problems, and sample differences in systematic review.

In the behavioral meta-analysis (on CU traits and substance use), we found that, although CU traits did not significantly associate with concurrent cannabis use, they did positively associate with concurrent use of alcohol and general drug use in adolescents. Longitudinal studies suggested CU traits positively associated with drug use over time. In addition, although this relationship with future substance use was weaker when conduct problems were accounted for, CU traits still contributed a significant effect independent of conduct problems. This finding, that CU traits predict future substance use independent of conduct problems, is of particular importance and is consistent with theory suggesting the impairment of social processes increase risk for SUD (Massey et al., 2017). Together with the systematic review, these findings call for further examination of positively valenced constructs (i.e. social cognition, theory of mind, empathy) to untangle specific socio-cognitive and -affective processes underlying adolescent substance use. Meta-analyses of these phenotypes will require more consistent measurement of social cognition and substance use outcomes across studies.

4.1 Gender Moderating Substance Use and CU Traits

Gender differences were not found for concurrent substance use in cross-sectional samples, but in longitudinal studies males have a stronger positive effect between CU traits and substance use compared to females. Males have been reported to have higher rates of CU traits than females, and CU traits as currently described may better capture male-centric aspects of this construct. Alternatively, it may be that males are, in part, at greater risk for increased substance use due to higher baseline levels of CU traits. A single study suggested that

CU traits were protective of substance use within females (Wymbs et al., 2012), Based on the available data, we can neither substantiate nor counter this claim in the present analysis, but some prior studies had a low proportion of males and those studies showed mixed results, with both significant and insignificant effects. The mediating effects of factors, such as emotional arousal or social perceptions, may be different for males and females. Additional studies are required to help us understand gender differences in relation to CU traits and future severity of substance use.

4.2 Study Sample Type Moderating CU Traits Association with Substance Use

Samples that were forensic/clinical compared to community samples had larger positive effects in longitudinal studies. This finding substantiated our hypothesis that forensic/clinical samples would have higher levels of socio- affective impairments and this would predict increased substance use over time. Importantly, the effect with the community sample was of a moderate size but not statistically significant – it is difficult to arrive at firm conclusions regarding the CU traits to substance use relationship in community samples. Further testing is needed to parse apart the multitude of processes (e.g. low affective arousal, less spontaneous perspective taking, impairments in sharing other's emotions) that may be specific to forensic and clinical samples.

4.3 Age Moderating CU Traits Relationship with Substance Use

Mean age of the sample did not moderate cross-sectional studies, but in longitudinal samples greater mean age was associated with higher effect sizes. This finding is within the curve of normative substance use that peaks during in late adolescents (Dennis & Scott, 2007; Rutherford et al., 2010). Although a valuable finding, it is plausible that this reflects a normative pattern of use that may decline as expected even in the presence of CU traits. Future studies that capture age ranges beyond the adolescent years will be important for determining whether CU traits may contribute to persistence in substance use beyond normative substance use patterns in adolescents.

4.4 Conduct Problem Controls Moderating CU Traits Relationship with Substance Use

In cross-sectional studies, controlling for conduct issues did not moderate the association between CU traits and substance use. Longitudinally, we demonstrated a significant moderation such that studies that did not control for conduct issues had a higher effect. However, it is important to note that studies that controlled for conduct issues still had a significant positive moderate effect. This suggests that CU traits account for some unique variance in predicting substance use longitudinally, independent of conduct problems. Massey and colleague's model (Massey et al., 2017), supports the importance of including moderators of response to social consequences and perception of use in future studies. Additionally, investigating the role that comorbid mental health symptoms or associated traits, such as anxiety and impulsivity, play in these relationships would similarly be important.

4.5 Neuroimaging Meta-Analysis

Neural differences were observed in adolescents identified at a high risk for SUD (or already having SUD) while engage in tasks related to social cognition. Some neural coordinates identified in our meta-analysis also are known to undergird social cognition and theory of mind (e.g., from search of the Neurosynth database). Notably, these regions did not have a strong association with maps of addiction. It may be that youth at this age do not yet show full neural patterns of addictions and these will later emerge. However, the neural differences in regions associating with social processes may indicate early warning signs for later substance use severity. This analysis did not find differences in subcortical regions such as the amygdala in the literature review. However, the studies included involved social tasks that are more likely to probe task-positive regions that are more cortical. Future studies could target subcortical regions to clarify this association with substance use. We found no longitudinal studies for the neural meta-analysis that examining tasks of social cognition and future risk of substance use. Such studies would be critical to develop models of neural development of social cognition in relation to substance use.

4.6 Limitations

The present findings must be interpreted in light of some limitations. First, in some analyses we consider single substance use (cannabis and alcohol) and in other analyses we considered general drug use. These choices were based on the available literature but also may limit the generalizability of our findings. Because this is a relatively new area of investigation, we had to examine multiple constructs that, although are overlapping, have

some conceptual and measurement differences. However, the consistent patterns of findings of an association across these constructs with substance use both cross-sectional and longitudinally suggest the robustness of these relationships. Additionally, the current review only identified a small number of studies for meta-analysis and our behavioral meta-analyses could only focus on CU traits.

5. Conclusion

The current systematic review suggests an association between social cognitive and affective constructs with both concurrent and future substance use. The relationship between positively valenced constructs and substance use phenotypes was consistently seen across gender and study sample type. Specifically, affective constructs appeared to negatively associate directly with substance use whereas cognitive constructs appeared to have an indirect effect through drug refusal efficacy. Thus, positively valenced socio-cognitive and -affective constructs appear to be multidimensional with important contributions to adolescent substance use. Differences were also shown in the brains of youth identified at a high risk versus controls. However, the systematic review of CU traits did not demonstrate consistent results relating to substance use.

The meta-analytic review was able to clarify some of these inconsistencies, showing moderate effect sizes between CU traits and both frequency of substance use concurrently and future substance use. We found differences in the presence of gender, sample type, controlling for conduct issues, and age. Of particular importance CU traits accounted for variance independently of conduct problems. Thus, these findings suggest socio-cognitive and -affective processes that are involved in substance use behavior in adolescents are multidimensional.

The present literature still leaves several questions to build on. Future studies could further examine the positively valenced constructs in relation to gender and sample type as well as test the indirect effects of socio-cognitive processes on drug refusal efficacy. Additionally, future studies should examine gender differences in the relationship between CU traits and future substance use. The meta-analysis revealed that samples with larger proportions of females had lower effect sizes (some studies were even insignificant), whereas all male studies had significant effects. This likely reflects some of the inconsistencies in the available literature. More studies are

needed to parse why females may show differences in social processes in relation to substance use. Overall, the present work provides evidence that socio-cognitive and -affective processes do predict substance use in adolescents. More work is needed to assess if causal effects exist.

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Figure titles and legends

Figure 1. Figure Depicting Effect Size Results of Behavioral Meta-Analysis.

Figure 2. Figure Depicting the Moderating Effect of Proportion of Males on Effect Sizes in Longitudinal Studies

Figure 3. Figure Depicting Moderating Effects of Controlling for conduct problems and Sample type

Figure 4. Figure Depicting Moderating Effect of Age on Effect Sizes in Longitudinal Studies

Figure 5. Figure Depicting Correlations of Neural Regions Meta-Analytic Neural Maps in Neurosynth

Supplemental Figure1. PRISMA flowchart of primary study selection.

Supplemental Figure 2. Figure Depicting Proportions of Publication Bias

Supplementary Figure 3. Figure Depicting Meta-Analysis Neural Differences in Youth at High SUD Risk from Controls

Tables 1 and 2 included in supplemental at end

Table 3. Summary of findings from meta-analysis findings

Outcome	N	*k*	Hedge's *g*	CI_{95}	Simulated Hedge's *g*
Cross-Sectional					
Alcohol[1]	1,612	6	0.32	0.01, 0.63	0.32
Cannabis	1,380	4	0.31	-0.03, 0.64	0.31
Drugs[1]	1,415	3	0.58	0.34, 0.82	0.58
Longitudinal					
Drugs	3,736	7	0.47	0.34, 0.60	0.47
Longitudinal: Gender					
Drugs	1,619	6	0.53	0.26,0.80	0.53

[1] = trim and fill model reported

Table 4. Estimates from models exploring moderation of the association between CU traits and substance use by study design and gender

Moderator	*b*	t	*p*
Cross-Sectional			
<u>Alcohol</u>			
Proportion: Male	0.00	1.27	0.42
Age	-0.08	-0.95	0.51
Sample: Forensic/Clinical	0.13	1.43	0.52
No Control: Conduct Problems	0.13	0.54	0.61
Design: Within-Subject	0.33	1.50	0.37
<u>Cannabis</u>			
Proportion: Male	0.00	1.28	0.42
Age	0.95	0.97	0.63
Sample: Forensic/Clinical	0.35	4.42	0.14
<u>Drugs</u>			
Proportion: Male	0.00	2.27	0.26
Age	-0.11	-0.60	0.55
Sample: Forensic/Clinical	0.30	0.59	0.55
No Control: Conduct Problems	0.17	0.46	0.65
Longitudinal			
<u>Drugs</u>			
Proportion: Male	0.00	2.55	0.00
Age	0.17	3.51	0.00
Sample: Forensic/Clinical	0.34	2.24	0.02
No Control: Conduct Problems	0.33	2.26	0.02
Design: Time Lag	-0.36	-0.86	0.38
Design: Timepoints	-0.08	0.40	0.68
Design: Time Lag x Timepoints	0.00	0.03	0.97

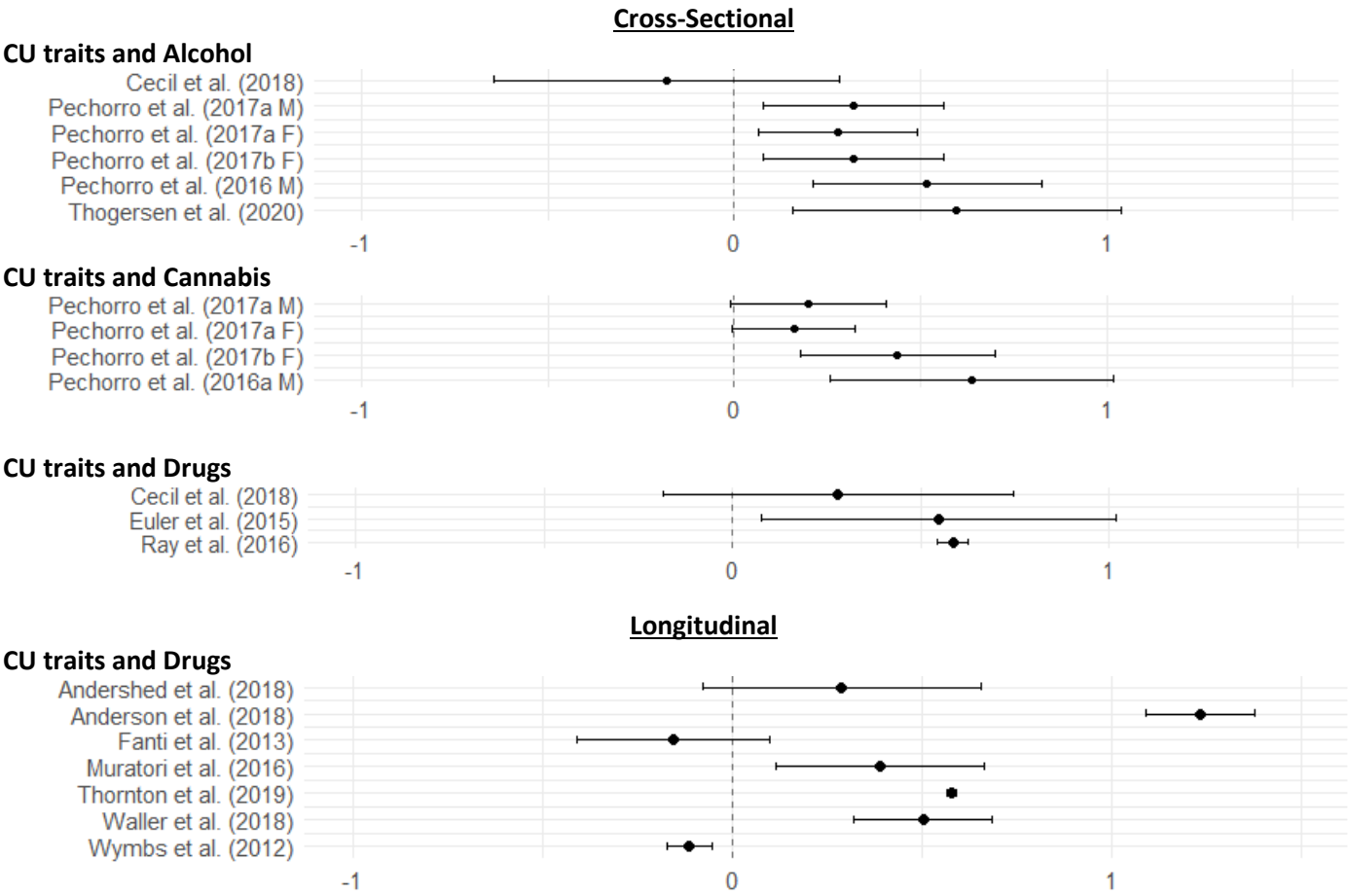


Figure 1. Figure Depicting Effect Size Results of Behavioral Meta-Analysis.

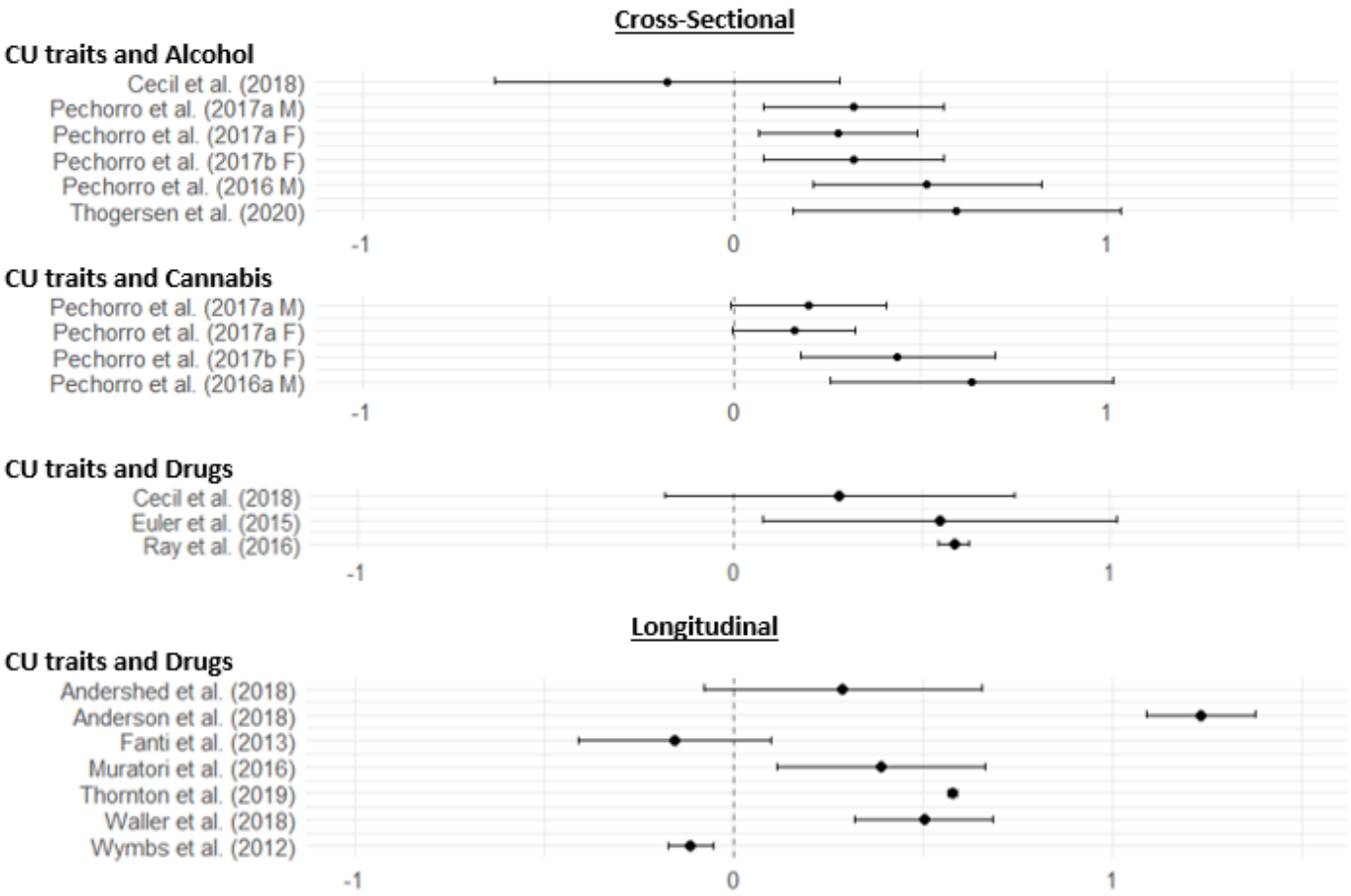


Figure 1. Figure Depicting Effect Size Results of Behavioral Meta-Analysis.

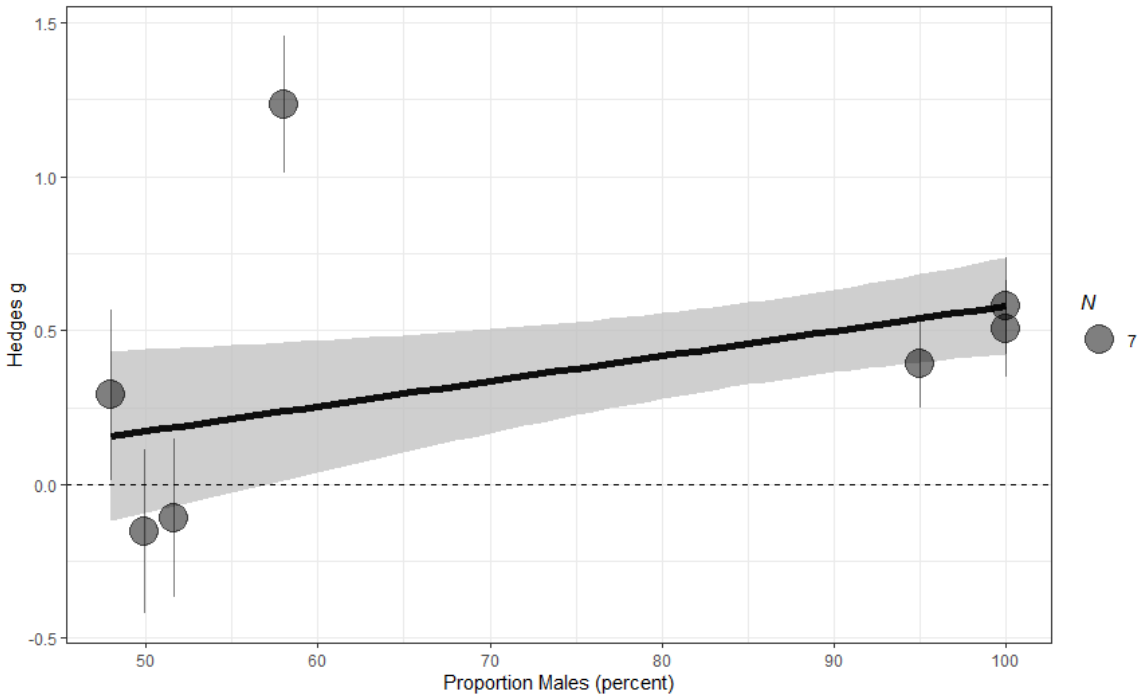


Figure 2. Figure Depicting the Moderating Effect of Proportion of Males on Effect Sizes in Longitudinal Studies

Moderating Longitudinal Effects CU Traits and Drugs

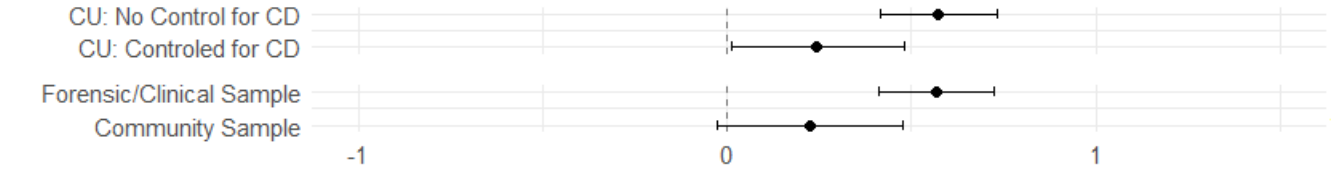


Figure 3. Figure Depicting Moderating Effects of Controlling for conduct problems and Sample type

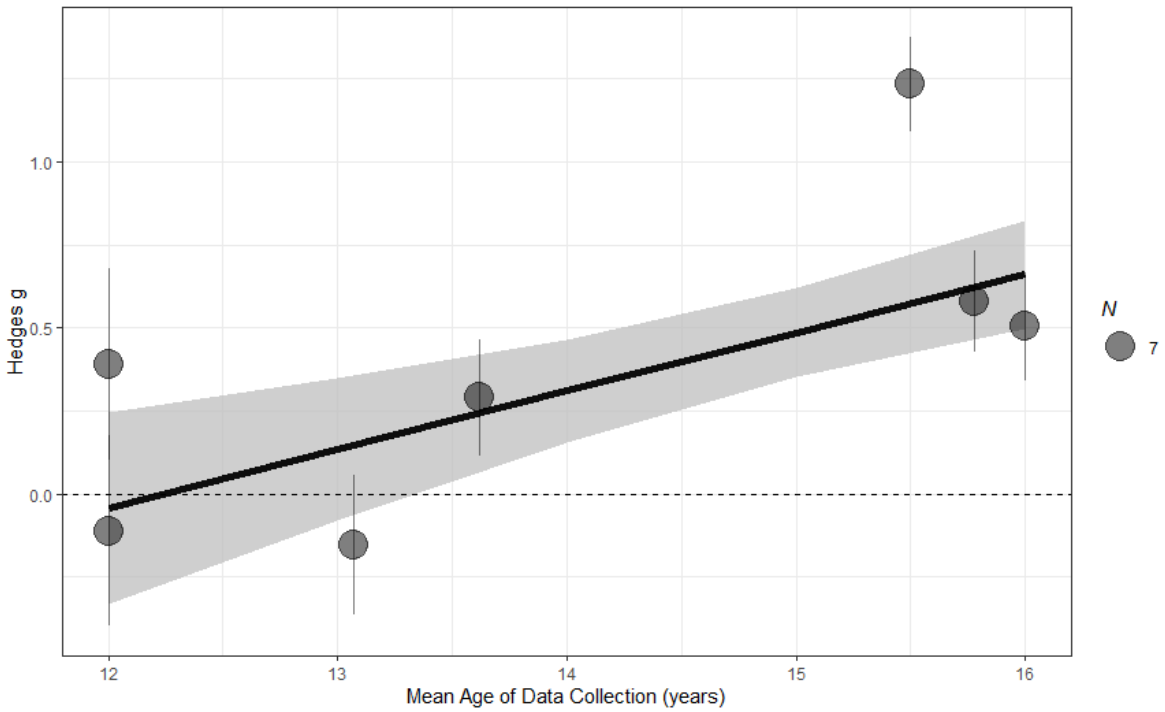


Figure 4. Figure Depicting Moderating Effect of Age on Effect Sizes in Longitudinal Studies

Table 5. Meta-Analysis of Neural Difference Between Youth at High Risk and Controls During Social Task and associations with neural maps

MNI Coordinates									
x	y	z	Hemisphere	Label	BA	ALE	Neural Map association (r)			
							Addict	Emp	SC	ToM
51	22	-8	Right	Orbital inferior frontal gyrus	47	0.0090	Addict	Emp	SC	ToM
-11	-63	1	Left	Lingual Gyrus	19	0.0097	--	--	--	--
21	-18	-37	Right	Parahippocampal gyrus	35	0.0102	--	--	--	--
3	4	11	Right	Caudate	--	0.0102	--	--	--	--
2	26	53	Right	Superior Frontal medial gyrus	8	0.0098	--	--	--	--
-21	-96	12	Left	Middle occipital gyrus	18	0.0094	--	--	--	--
-62	-26	13	Left	Superior temporal gyrus	41	0.0094	--	--	--	--
38	-76	19	Right	Middle occipital gyrus	19	0.0094	--	--	--	--
10	61	26	Right	Superior Frontal medial gyrus	9	0.0094	0.01	0.08	0.39	0.43
-9	-82	46	Left	Superior occipital lobe	7	0.0094	0.02	-0.03	0.10	0.18
-39	24	45	Left	Frontal medial gyrus	8	0.0098	--	--	--	--
49	-72	34	Right	Angular gyrus	39	0.0098	-0.01	-0.06	-0.23	-0.23
-58	-35	47	Left	Inferior parietal lobule	40	0.0094	--	--	--	--
-58	13	-16	Left	Superior temporal pole	38	0.0102	--	--	--	--

All coordinate anatomical likelihood estimations have an FDR corrected p value of < .001

-- = no association

Addict = addiction map; Emp= Empathy map; SC= Social cognition map; ToM = Theory of mind map

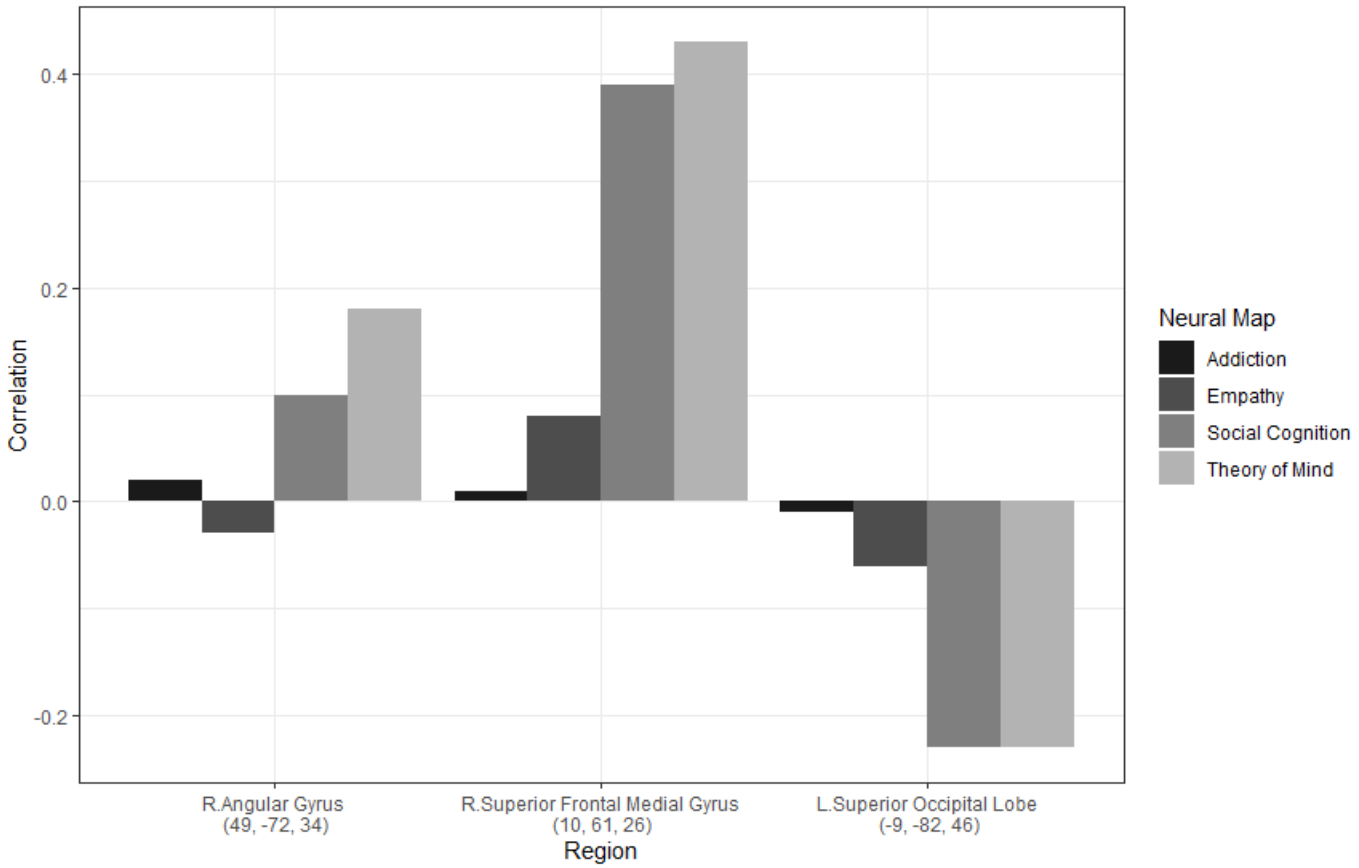


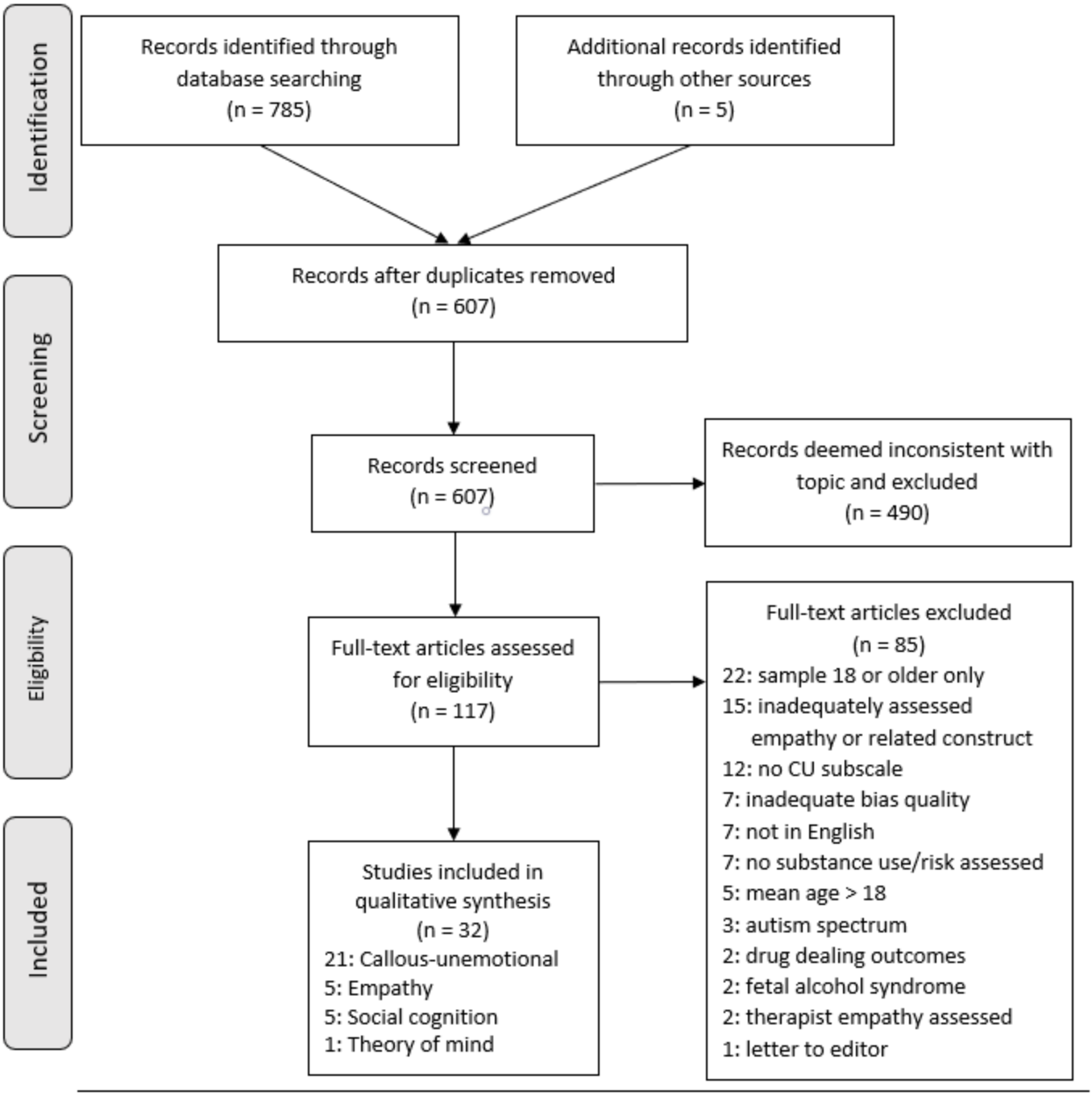
Figure 5. Figure Depicting Correlations of Neural Regions Meta-Analytic Neural Maps in Neurosynth

SUPPLEMENTAL

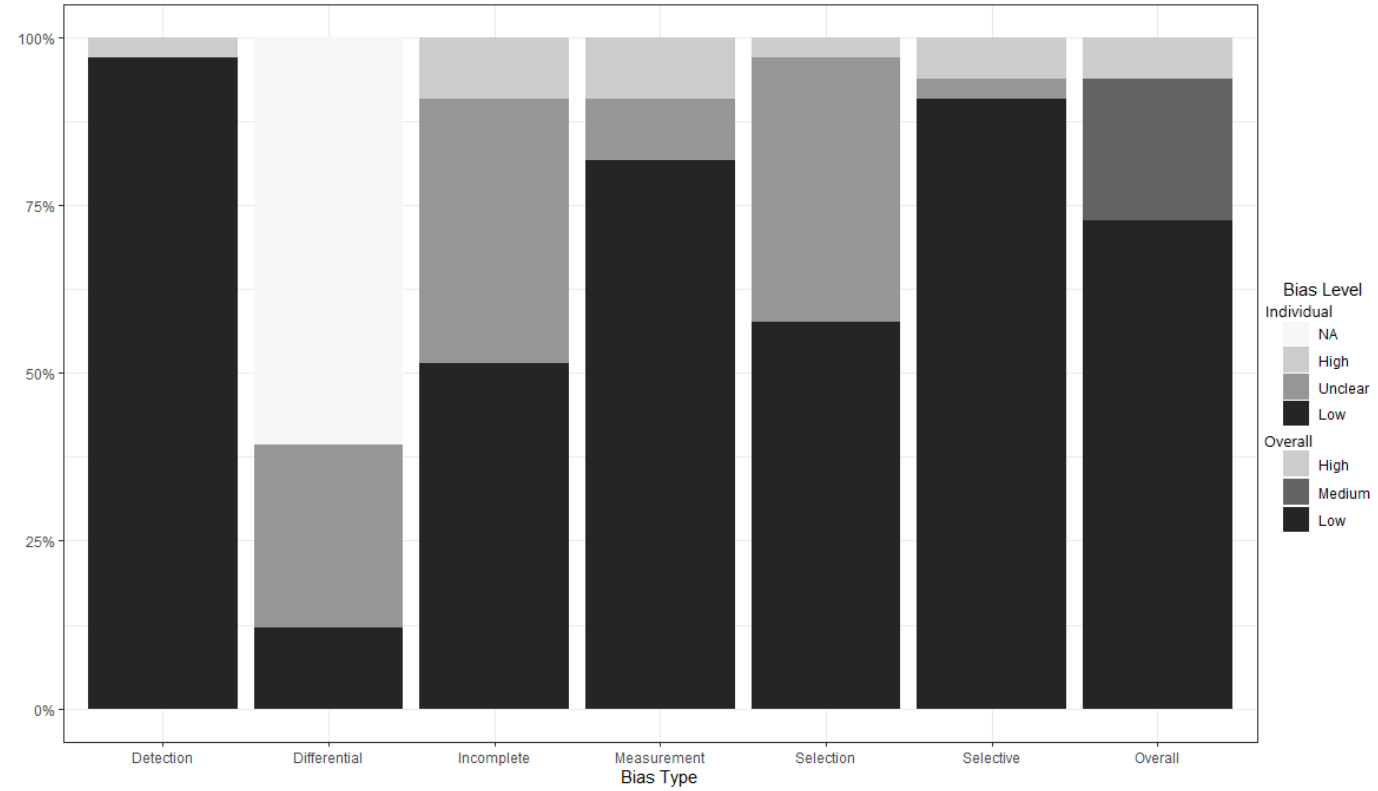
Supplemental Table 1
Literature Search Keywords

Terms for	
Social Constructs	**Substance Use**
Empathy	Substance-Related Disorders
Theory of mind	Drug abuse
Social cognition	Substance use
Callous-unemotional traits	Addiction
	Risk
	Alcohol/Alcoholism
	Marijuana
	Cannabis
	Tobacco
	Cigarette
	Opioid/Opiate/Heroin
	Abuse/Addiction/Dependence/Use/Use Disorder

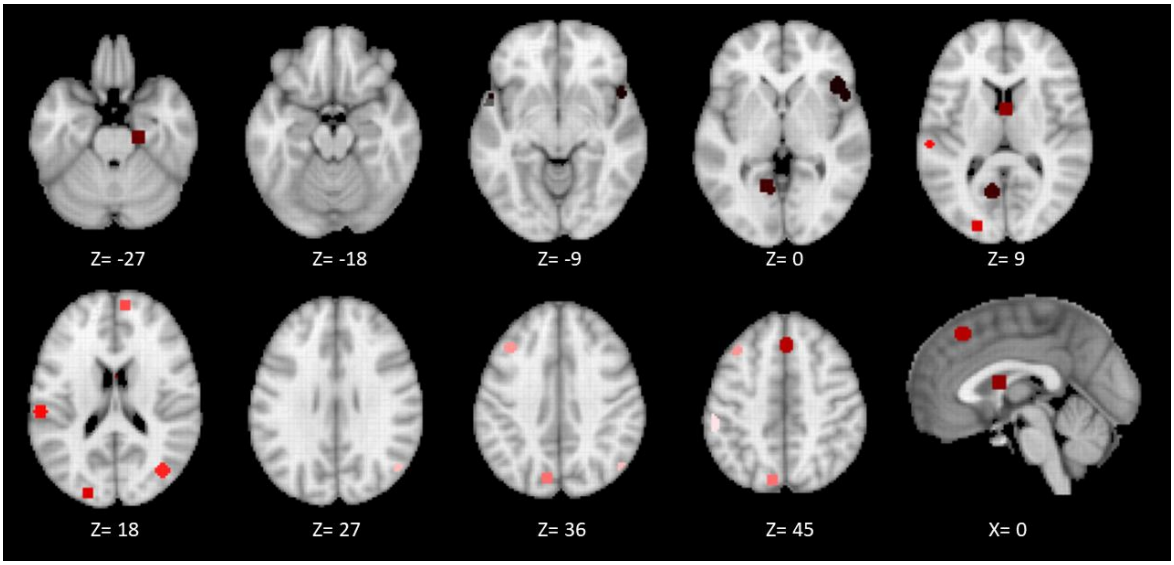
Filtered by: Age (child 6-12 & adolescent 12-18), publication data (1/1/1982 – 9/11/2020), and English



Supplemental Figure 1. PRISMA flowchart of primary study selection.



Supplemental Figure 2. Figure Depicting Proportions of Publication Bias



Supplementary Figure 3. Figure Depicting Meta-Analysis Neural Differences in Youth at High SUD Risk from Controls

Supplemental Table 2. Risk of bias for each study

	Selection bias	Measurement bias	Detection bias	Differential attrition	Incomplete outcome data [a]	Selective reporting	Overall bias
Andershed et al. (2018)	low	low	low	unclear	unclear	low	low
Anderson et al. (2018)	unclear	low	low	low	unclear	low	low
Anh et al. (2011)	low	high	low	*NA*	low	high	high
Baskin-Sommers et al. (2015b)	unclear	low	low	unclear	unclear	unclear	medium
Cecil et al. (2017)	unclear	low	low	*NA*	low	low	low
Chabrol et al. (2012)	low	low	low	*NA*	low	low	low
Cservenka et al. (2014)	unclear	low	low	*NA*	low	low	low
Dubas et al. (2017)	unclear	low	low	unclear	high	low	medium
Euler et al. (2015)	unclear	low	low	*NA*	low	low	low
Fanti (2013)	low	low	low	unclear	high	low	medium
Ferreira et al. (2012)	low	low	low	*NA*	unclear	low	low
Fluharty et al. (2018)	unclear	unclear	high	unclear	high	high	high
Hulvershorn et al. (2013)	unclear	low	low	*NA*	unclear	low	low
Hyde et al. (2015)	low	unclear	low	*NA*	low	low	low
Kirisci et al. (2004)	low	low	low	unclear	unclear	low	low
Laghi et al (2019)	unclear	low	low	NA	unclear	low	low
Lannoy et al. (2020)	unclear	high	low	NA	low	low	medium
Luengo et al. (1994)	unclear	unclear	low	*NA*	low	low	low
Muratori et al. (2016)	low	low	low	low	unclear	low	low
O'Brien and Hill (2017)	unclear	low	low	*NA*	unclear	low	low
Pechorro, da Silva, et al. (2016)	low	low	low	*NA*	low	low	low
Pechorro, da Silva, et al. (2017)	low	low	low	*NA*	low	low	low
Pechorro, Gonçalves, et al. (2017)	low	low	low	*NA*	low	low	low
Pechorro, Hawes, et al. (2017)	low	low	low	*NA*	low	low	low
Pechorro, Ray, et al. (2016)	low	low	low	*NA*	low	low	low
Ray et al. (2016)	low	low	low	*NA*	low	low	low
Sakai et al. (2017)	low	low	low	*NA*	low	low	low
Thogersen et al. (2020)	low	low	low	low	low	low	low
Thornton et al. (2019)	low	low	low	low	low	low	low
Waller et al. (2018)	unclear	low	low	unclear	unclear	low	medium
Winters et al. (2020)	low	low	low	low	unclear	low	medium
Wymbs et al. (2012)	low	high	low	unclear	unclear	low	medium

[a] for cross-sectional studies criteria for incomplete outcome data are if missing participants has potential to affect results