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Adolescent impulsivity phenotypes characterized by distinct brain networks

Robert Whelan[1,2], Patricia J Conrod[3,4], Jean-Baptiste Poline[5], Anbarasu Lourdusamy[3], Tobias Banaschewski[6], Gareth J Barker[3], Mark A Bellgrove[7], Christian Büchel[8], Mark Byrne[2], Tarrant D R Cummins[7], Mira Fauth-Bühler[9], Herta Flor[10], Jürgen Gallinat[11], Andreas Heinz[11], Bernd Ittermann[12], Karl Mann[9], Jean-Luc Martinot[13,14], Edmund C Lalor[2], Mark Lathrop[15], Eva Loth[3,16], Frauke Nees[10], Tomas Paus[17–19], Marcella Rietschel[20], Michael N Smolka[21,22], Rainer Spanagel[23], David N Stephens[24], Maren Struve[10], Benjamin Thyreau[5], Sabine Vollstaedt-Klein[9], Trevor W Robbins[25], Gunter Schumann[3,16], Hugh Garavan[1,2] & the IMAGEN Consortium[26]

The impulsive behavior that is often characteristic of adolescence may reflect underlying neurodevelopmental processes. Moreover, impulsivity is a multi-dimensional construct, and it is plausible that distinct brain networks contribute to its different cognitive, clinical and behavioral aspects. As these networks have not yet been described, we identified distinct cortical and subcortical networks underlying successful inhibitions and inhibition failures in a large sample (n = 1,896) of 14-year-old adolescents. Different networks were associated with drug use (n = 1,593) and attention-deficit hyperactivity disorder symptoms (n = 342). Hypofunctioning of a specific orbitofrontal cortical network was associated with likelihood of initiating drug use in early adolescence. Right inferior frontal activity was related to the speed of the inhibition process (n = 826) and use of illegal substances and associated with genetic variation in a norepinephrine transporter gene (n = 819). Our results indicate that both neural endophenotypes and genetic variation give rise to the various manifestations of impulsive behavior.

Adolescence is a time of expanding boundaries and testing limits, which often includes impulsive, and perhaps risky, behavior. Such risk-taking is a normal part of development, is common across mammalian species and is likely a result of evolutionary pressures to acquire the skills necessary to move from dependence to independence[1]. However, the failure to inhibit inappropriate behaviors may have undesirable consequences. Adolescent mortality, in the industrialized world, is primarily a result of preventable and/or self-inflicted causes that may, in part, be related to impulsive, risk-taking behavior[2]. For example, poor inhibitory control is a risk factor for problematic substance experimentation in early adolescence, which in turn correlates with substance misuse in late adolescence and adulthood[3]. Furthermore, animal models of substance misuse show that administration of drugs during adolescence has deleterious and long-lasting neurotoxic effects on the developing brain, particularly on frontal lobe functioning[4]. Thus, understanding the brain processes associated with inhibitory control in human adolescents represents an important challenge for neuroscientists, with wider implications for adolescent public health.

As noted, impulsivity is a risk factor for drug use in early adolescence, and exploratory use of alcohol is normative by approximately 14 years of age in the US[5]. Poor inhibitory control is also a feature of attention-deficit hyperactivity disorder (ADHD), the most common neurodevelopmental psychiatric disorder. Although the symptoms of

[1]Departments of Psychiatry and Psychology, University of Vermont, Burlington, Vermont, USA. [2]Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland. [3]Institute of Psychiatry, King's College London, London, UK. [4]Department of Psychiatry, Université de Montreal, CHU Ste Justine Hospital, Montreal, Canada. [5]Neurospin, Commissariat à l'Energie Atomique, Gif-sur-Yvette, France. [6]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany. [7]Queensland Brain Institute and School of Psychology, The University of Queensland, St. Lucia, Australia. [8]Universitaetsklinikum Hamburg Eppendorf, Hamburg, Germany. [9]Department of Addictive Behaviour and Addiction Medicine, Central Institute of Mental Health, Mannheim, Germany. [10]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. [11]Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitätsmedizin Berlin, Berlin, Germany. [12]Physikalisch-Technische Bundesanstalt, Berlin, Germany. [13]Institut National de la Santé et de la Recherche Médicale, INSERM CEA Unit 1000 'Imaging & Psychiatry,' University Paris Sud, Orsay, France. [14]Assistance Publique Hopitaux de Paris Department of Adolescent Psychopathology and Medicine, Maison de Solenn, University Paris Descartes, Paris, France. [15]Centre National de Génotypage, Evry, France. [16]MRC Social, Genetic and Developmental Psychiatry Centre, London, UK. [17]Rotman Research Institute, University of Toronto, Toronto, Canada. [18]School of Psychology, University of Nottingham, Nottingham, UK. [19]Montreal Neurological Institute, McGill University, Montreal, Canada. [20]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany. [21]Department of Psychiatry and Psychotherapy, Technische Universität, Dresden, Germany. [22]Neuroimaging Center, Department of Psychology, Technische Universität, Dresden, Germany. [23]Institute of Psychopharmacology, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany. [24]Department of Psychology, University of Sussex, Sussex, UK. [25]Behavioral and Clinical Neuroscience Institute and Department of Experimental Psychology, University of Cambridge, Cambridge, UK. [26]Institute of Psychiatry, King's College London, London, UK. Correspondence should be addressed to R.W. (robert.whelan@uvm.edu) or H.G. (hugh.garavan@uvm.edu).

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ADHD can ameliorate with age, the continuing presence of ADHD symptoms into adolescence conveys increased risk for negative outcomes, such as academic underperformance and interpersonal difficulties[6]. However, the link between ADHD and adolescent substance misuse is unclear, and determining the nature of this relationship represents a challenge (for example, adults who misuse substances are more likely to retrospectively endorse childhood ADHD symptoms)[7].

Impulse control is often measured using the stop-signal task (SST), which requires the participant to cancel an already initiated motor response[8]. The time required to stop a response, the stop-signal reaction time (SSRT), is extensively used as a clinical index of impulse control. In particular, participants with ADHD have longer SSRTs[9], as do chronic users of cocaine[10] and individuals with alcohol dependence[11]. In adults, it is known that the right inferior frontal gyrus and basal ganglia are important in action-cancellation tasks, such as the SST, although the relative roles of the subcomponents of the stopping network have not been fully characterized[12]. It is important to note, however, that the adolescent brain, particularly the frontal lobe, is still maturing, which is a process that involves a decrease in gray matter as a result of synaptic pruning and possibly an increase in white matter as a result of myelination, which in turn results in increased specialization by adulthood[13]. Comparison of adolescents and adults has revealed a similar pattern of activation on inhibition tasks, albeit with greater levels of activity in adolescents[14]. Thus, impulse control networks in adolescents cannot necessarily be inferred from studies using adults.

Although impulsivity is a multi-dimensional construct incorporating the inability to wait, insensitivity to negative consequences and distractibility, an inability to inhibit unwanted behaviors is central to most definitions[15,16]. Co-morbidity rates between different facets of impulsive behavior, although high, are not perfect, suggesting that distinct brain networks may contribute to the cognitive, clinical and behavioral elements of impulsivity. Relating these subcomponents (putative neural endophenotypes) to particular genotypes or phenotypes, such as individual differences in SSRT, substance abuse or psychiatric symptoms, is challenging, not least because a large sample size is required to adequately identify the networks involved and then to relate these networks to phenotypes.

In this study, we sought to identify the brain networks involved in inhibitory control in early adolescence. In addition, we attempted to determine the extent to which individual differences in SSRT, ADHD symptoms, substance misuse and genetics are associated with these networks. There is, for example, considerable controversy about whether ADHD symptoms represent a predictive endophenotype for subsequent drug abuse[17]; this hypothesis would predict some commonality in the mechanisms contributing to impulsive behavior. Although both drug abuse and ADHD are associated with impaired stop-signal performance, it is possible that both types of impulsivity deficits are derived from distinct brain networks. We applied factor analysis to a large sample (n = 1,896) of adolescents performing the SST. The advantage of factor analysis over the mass univariate approach typically employed in functional magnetic resonance imaging (fMRI) studies is that biologically relevant networks of interdependent, rather than single, regions of interest can be identified. This was achieved by exploiting individual differences in activation levels afforded by the large sample size.

RESULTS

Neural networks supporting SST performance

The factor analysis results identified seven networks for stop success (**Fig. 1**) and six networks for stop failure (**Fig. 2** and **Supplementary Tables 1–4**). The separate subcortical, frontal, parietal and motor networks were anatomically plausible and broadly concordant with previous studies of inhibition in adults[18–20]. Factor scores, calculated using a regression method that weighted each participant's region of interest (ROI) score according to the factor loading matrix, showed the average correlation among factors to be low (mean absolute r of 0.172 and 0.189 for stop success and stop fail networks, respectively), highlighting their relative independence. The validity of the factor analysis approach is reflected in the finding that spatially separated, but functionally inter-related, regions were grouped in the same network (for example, left and right parietal cortices) and that it was possible to distinguish among adjacent regions (for example, the subthalamic nucleus (STN) from thalamus).

The functional relevance of these brain networks was next assessed by examining their relationship to clinically relevant, individual differences in inhibitory control in a set of statistical comparisons using empirically derived P values from 10,000 bootstrap samples, which gives an accurate estimate of the replicability of the result (the exact P values from each statistical test, without correction for multiple comparisons, are provided). Each comparison controlled for age, sex, handedness, scan site, verbal IQ and performance IQ.

Individual differences in network activations and SSRT

The proportion of successful stop trials across all participants was 57 ± 7% (mean ± s.d.). For those participants included in the SSRT analysis, the mean SSRT was 219 ± 39 ms, the mean Go reaction time (Go RT) was 429 ± 63 ms and the mean Go RT variability (that is the s.d. of each participant's Go RT) was 102.49 ± 25.21 ms. We divided the SSRT data according to a median split and compared the upper (mean SSRT, 249.20 ± 24.05 ms) and lower medians (mean SSRT, 189.15 ± 26.13 ms). There were significant differences for the stop fail bilateral frontal network ($F_{1,801}$ = 9.424, P = 0.0020), the stop success

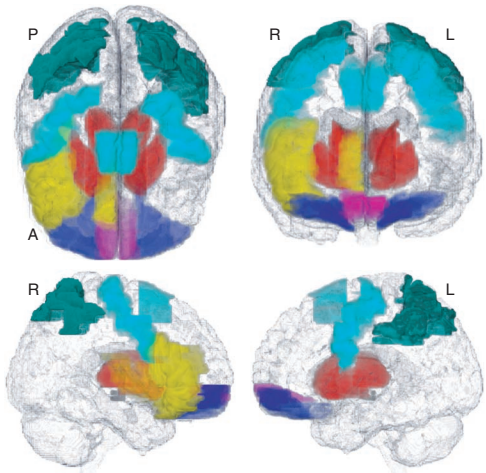

Figure 1 A graphical representation of the stop success networks (that is, areas active during trials on which subjects successfully inhibited an already initiated motor response). For ease of communication, we assigned these networks labels derived from their most prominent anatomical locations: bilateral putamen, caudate, pallidum and thalamus (stop success basal ganglia network, red), right inferior frontal gyrus (IFG), right insula and right anterior cingulate (stop success right frontal network, yellow), bilateral substantia nigra and STN (stop success substantia nigra/STN network, gray), bilateral superior and middle orbital gyri (stop success orbital network, violet), bilateral pre-SMA/PCG (stop success pre-SMA/PCG network, cyan), bilateral inferior and superior parietal lobes (stop success parietal network, dark blue), and bilateral medial orbital gyri (stop success medial orbital network, magenta). A, anterior; L, left; P, posterior; R, right.

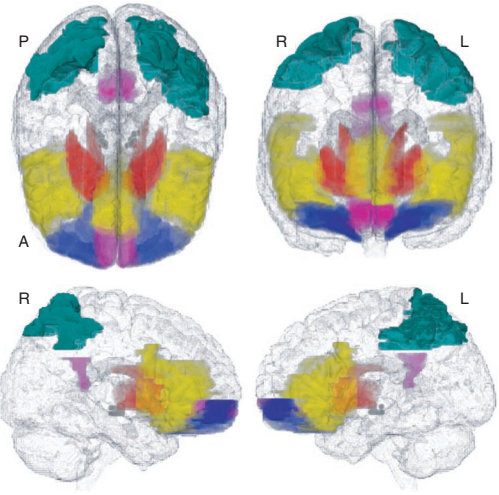

Figure 2 A graphical representation of the stop fail networks (that is, areas active during those trials on which subjects failed to inhibit an already initiated motor response). The stop fail networks were networks involving areas considered to be key elements of the brain's performance monitoring system, including the anterior cingulate, insula and IFG (stop fail bilateral frontal network, yellow), bilateral substantia nigra and STN (stop fail substantia nigra/STN network, gray), bilateral putamen, caudate and pallidum (stop fail basal ganglia network, red), bilateral inferior and superior parietal lobes (stop fail parietal network, dark blue), bilateral posterior cingulate and medial orbital gyrus (PCC/medial orbital gyri network, magenta), and bilateral superior and middle orbital gyri (stop fail orbital network, violet).

right frontal network ($F_{1,806} = 16.512$, $P = 0.0001$) and the stop success basal ganglia network ($F_{1,799} = 6.494$, $P = 0.0131$) with higher brain activity for participants with faster SSRTs (**Fig. 3**).

To date, evidence for the neural correlates of SSRT in adults has been inconsistent. A previous study analyzed the grouped data of 126 subjects by conducting an independent component analysis using data from five studies and found two components correlated with SSRT that survived correction for multiple comparisons[20]. These two components included numerous brain regions (for example, one component incorporated frontal operculum, insula, orbital cortex, precentral gyrus, paracingulate, anterior cingulate cortex, occipital, temporal and subcortical regions) and therefore did not localize SSRT to a specific structure or circuit. Another study using independent component analysis[19] tested for, but failed to find, any correlations with SSRT. Notably, we did not find that the stop success substantia nigra/STN network was differentially associated with SSRT ($F_{1,797} = 0.0008$, $P = 0.977$), in contrast with previous findings[21] (comparing six versus seven participants). Finally, it was shown that the left superior frontal gyrus, precentral gyrus and anterior cingulate were differentially associated with SSRT performance[22]. However, this result was uncorrected for multiple comparisons across voxels and compared 12 participants per group.

It has been shown that SSRT can be affected by Go RT variability[23], rather than mean Go RT, possibly arising from fluctuations in sustained attention. We divided participants according to a median split on the standard deviation of their Go RT (entering mean Go RT as an additional nuisance variable). The stop fail bilateral frontal network was significantly different ($F_{1,804} = 9.554$, $P = 0.0029$), with more activation associated with less variability. A considerable body of evidence links this network to performance monitoring processes; this quite plausibly explains why those with relatively lower activation in this network would show more variable performance monitoring leading to increased performance variability (and, as noted, increased SSRTs). There were also performance variability differences for both the stop success posterior cingulate cortex (PCC)/medial orbital network ($F_{1,808} = 9.328$, $P = 0.0026$; more activation was associated with more Go RT variability) and the stop fail medial orbital network ($F_{1,804} = 10.182$, $P = 0.0016$; more activation was associated with more Go RT variability). The stop success PCC/medial orbital and stop fail medial orbital network represent components of the default-mode network[24], a network of brain regions that are more active when a person is not engaged in exogenously driven, goal-directed behavior. An increase in activity in the default-mode network for participants with greater variability suggests that these participants are not able to allocate sufficient cognitive resources to the SST to sustain consistent performance[25]. It is notable that the stop success right frontal and stop success basal ganglia networks that were related to SSRT were not related to Go variability. Thus, the impulse control required by this task emerges from an interaction between brain regions that influence the Go process and distinct regions associated with the stopping process (also see **Supplementary Table 5**).

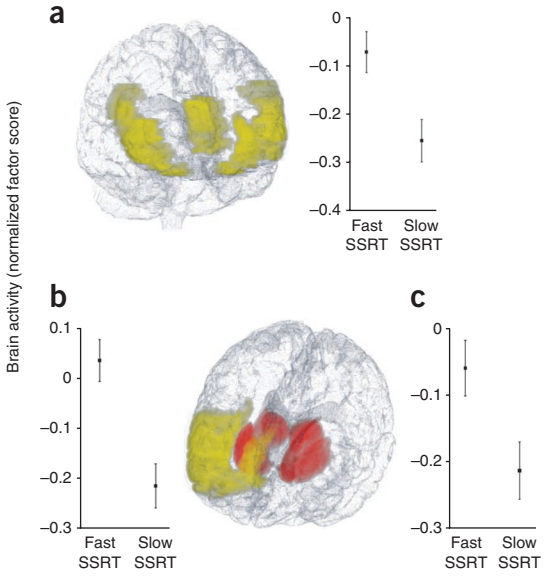

Figure 3 A graphical representation of the SSRT results showing the anatomical locations of the relevant factors and the mean reaction time. (**a**–**c**) Stop fail bilateral frontal network (yellow, **a**), stop success right frontal network (yellow, **b**) and stop success basal ganglia network (red, **c**). Error bars represent ±1 s.e.m.

Relationship of stop task networks with substance misuse

As suggested above, poor inhibitory control during the adolescent years may be especially relevant to problematic substance experimentation and use. First, we identified participants who had used any substance (either alcohol, nicotine or illicit substances) and compared them with participants who had never used any of these substances (ADHD symptom score was an additional covariate in these substance misuse analyses). The stop success orbital network was significantly less active for participants who had misused any substances ($F_{1,1578} = 7.913$, $P = 0.0036$). Next, we sorted participants into four groups: those who had never tried alcohol, nicotine or illicit substances (group 0, $n = 346$), those who had tried either alcohol or nicotine (group 1, $n = 775$), those who had tried alcohol and nicotine (group 2, $n = 324$), and those who had tried alcohol, nicotine and

at least one illicit substance (group 3, $n = 99$). There were significant substance use effects for the stop success orbital ($F_{3,1527} = 2.897$, $P = 0.0340$), stop success right frontal ($F_{3,1533} = 3.483$, $P = 0.0153$), and stop success pre–supplementary motor area (pre-SMA; $F_{3,1521} = 2.818$, $P = 0.0379$) networks (**Fig. 4**). *Post hoc* tests showed that for the stop success pre-SMA network group 1 differed from group 2 ($P = 0.0118$) and that there was a trend towards a difference between group 0 and group 2 ($P = 0.0671$; **Fig. 4b**). *Post hoc* tests for the stop success right frontal network showed that group 3 had significantly more activation than groups 0, 1 and 2 ($P = 0.0038$, $P = 0.0016$ and $P = 0.0023$, respectively; **Fig. 4c**). *Post hoc* tests for the stop success orbital network showed significant differences between group 0 and group 1 ($P = 0.0086$), between group 0 and group 2 ($P = 0.0141$) and trended towards significance for group 0 versus group 3 ($P = 0.0758$), with less activation for the substance misuse group in each case (**Fig. 4d**). The effect in the stop success orbital network held even when comparing non-users to those with four or fewer lifetime uses of alcohol ($P = 0.0022$), suggesting that orbital hypoactivity may be a potential vulnerability factor for alcohol use[26].

In contrast with the stop success orbital and pre-SMA/precentral gyrus (PCG) networks, only the stop success right frontal network activation differed between group 3 (those who had used alcohol and nicotine and illicit substances) and the other groups. It is therefore plausible that the effect in the right frontal network was associated with illicit substance use *per se* and with the severity of illicit substance use. We compared participants who never used illicit substances with participants with medium illicit substance use (one to four lifetime uses) and participants with high illicit substance use (five or more lifetime uses) on this right frontal network, controlling for any alcohol and cigarette use by adding them as nuisance variables. There was a significant effect of illicit substance abuse level ($F_{2,1578} = 7.380$, $P = 0.0006$). *Post hoc* tests showed a significant difference between non-users versus medium users ($P = 0.0356$), non-users versus high users ($P = 0.0004$) and medium users versus high users ($P = 0.0280$), with activation increasing with drug use (**Fig. 4a**; also see **Supplementary Tables 6–8**).

Relationship of stop task networks with ADHD symptoms

Impaired cognitive control is a feature of ADHD and we tested for the presence of these features in a non-clinical sample showing relatively low levels of ADHD-like symptoms. We identified 171 participants with subclinical features of ADHD (see Online Methods) and matched each of them with a control participant (ADHD = 0, and matched for age, sex, handedness, site, verbal and performance IQ, obsessive-compulsive disorder symptomatology, and as closely as possible on drug use). However, a χ^2 analysis revealed that participants with ADHD symptoms were significantly more likely to have tried nicotine and illicit substances ($P < 0.05$). Thus, we entered use of alcohol, nicotine and illicit substances as nuisance covariates to remove their influence. Participants with ADHD symptoms and control participants did not differ significantly ($P > 0.05$) on SSRT or Go RT variability (**Supplementary Table 9**). There were no significant differences between the groups on activation for stop success trials ($P > 0.05$ in all cases). However, there were significant differences for the stop fail bilateral frontal network ($F_{1,341} = 6.137$, $P = 0.0137$) and the stop fail basal ganglia network ($F_{1,342} = 4.698$, $P = 0.0309$), with reduced activity in both in participants with subclinical features of ADHD. The finding that both frontal and subcortical areas are implicated in subclinical ADHD symptoms is consistent with observations made in clinical ADHD samples[27]. Moreover, the finding that only stop fail networks differentiated between participants with ADHD symptoms and matched controls provides additional evidence that performance monitoring deficits may be an important feature of this disorder[28]. Notably, these findings also suggest a degree of independence at the neural level for the deficits in inhibitory control associated with ADHD and the propensity for drug abuse.

As there were relatively few adolescents with ADHD symptoms who also misused substances (and vice versa), we compared participants with ADHD symptoms on networks implicated in substance misuse and substance misusers on networks implicated in ADHD. The stop success orbital frontal, right frontal and pre-SMA/PCG networks (all implicated in drug abuse) were compared for the ADHD symptom group versus the control group: these comparisons were not significant (orbital frontal, $t_{347} = 0.049$, $P = 0.960$; right frontal, $t_{350} = 0.794$, $P = 0.416$; pre-SMA/PCG, $t_{345} = 0.585$, $P = 0.557$; use of alcohol, nicotine and illicit substances were entered as nuisance covariates). A comparison of the stop fail bilateral frontal and basal ganglia networks (different for those with ADHD symptoms versus those with no symptoms) were not different between those who had misused alcohol, nicotine or illegal substances versus those who had never misused any substance ($F_{1,1562} = 1.891$, $P = 0.169$ and $F_{1,1579} = 0.041$, $P = 0.840$, respectively).

Genetic results

Although the emerging personality of an adolescent is likely driven by multiple environmental factors, genetic influences also predispose towards impulsivity[29,30]. It has recently been shown[31] that, compared with healthy volunteers, SSRT was significantly higher for individuals with drug dependence and their non-dependent siblings, consistent with a hereditary component to inhibitory control as indexed by SSRT. Both norepinephrine and dopamine have been shown to be important for inhibitory control[32].

We found that allelic variation in *rs36024*, a single nucleotide polymorphism (SNP) located in intron 4 of the *SLC6A2* gene, which encodes the norepinephrine transporter (NET), was significantly

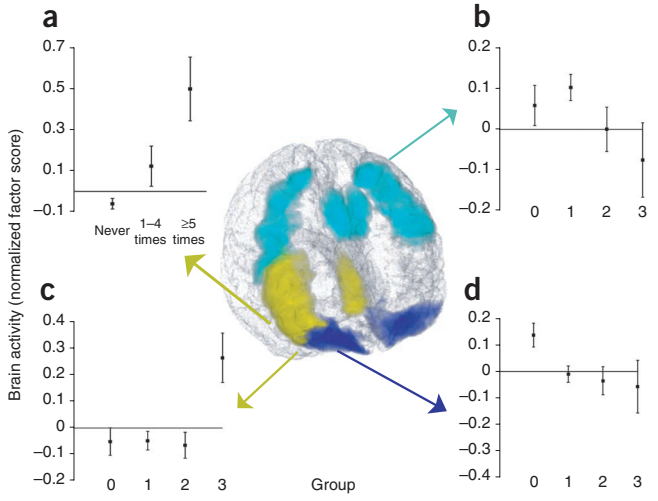

Figure 4 A graphical representation of substance misuse results. (**a**) The mean factor score for those who had never tried illicit substances, those with four or fewer lifetime uses, and those with five or more lifetime uses, with use of alcohol and nicotine as nuisance variables. (**b**–**d**) Mean factor scores for those who had never tried alcohol, nicotine or illicit substances, those who had tried either alcohol or nicotine, those who had tried alcohol and nicotine, and those who had tried alcohol, nicotine and at least one illicit substance (groups 0, 1, 2 and 3, respectively) for the pre-SMA/PCG, right frontal and stop success orbital networks. Error bars represent ±1 s.e.m.

associated with activity in the stop success right frontal network, with activity increasing additively with each copy of the T allele (that is, from the CC to CT to TT allelic variants of *rs36024*; significant at $\alpha = 0.05$, corrected for multiple related comparisons, after 100,000 random permutations, $\eta_{sp}^2 = 0.0144$). The robustness of this effect is bolstered by the finding that 4 of the 22 remaining SNPs in *SLC6A2* were also associated ($P < 0.05$) with right frontal stop success activity (note that these SNPs did not survive our conservative criterion for multiple comparison correction; **Supplementary Table 10**). Notably, these SNPs were not in high linkage disequilibrium with *rs36024* (**Supplementary Table 11**), indicating that their effects were not driven by shared variance with *rs36024* (also see **Supplementary Table 12**). Our result is consistent with pharmacological data in rodents and in humans that selective norepinephrine reuptake inhibitors improve inhibitory control and modulate inhibition-related activity in the inferior frontal gyrus[33].

DISCUSSION

Adolescence is a critical period in development in which behavioral tendencies and personalities that extend into adulthood are established. Many psychological disorders emerge during this period, with several of them exhibiting impulse control as a defining feature. Employing a large sample size (the largest single imaging study of either adolescents or adults) allowed us to describe the neurobiology of impulse control in early adolescence by identifying brain regions that work together in functionally meaningful networks. Furthermore, we demonstrated the clinical utility and potential of this analysis by determining how different networks relate to substance misuse and subclinical ADHD, as well how a subset of these networks relate to a genetic polymorphism affecting norepinephrine transmission.

We found a finite number of distinct, reproducible, independent and biologically plausible networks. The inter-individual variance in the functioning of these networks provides insights into different impulsivity phenotypes that are not readily discerned with the behavioral measures. For example, although clearly related to different stop success networks, there were no significant differences in the SSRTs of individuals with or without subclinical ADHD, nor for those who had used alcohol, nicotine or illicit substances versus those who had not misused any substances. Conversely, the neural endophenotypes were able to distinguish among those with and without ADHD symptoms (stop fail bilateral frontal and stop fail basal ganglia networks), and those who had used alcohol, nicotine or illicit substances (the stop fail orbital frontal network) versus those who had not misused any substances.

The factor analysis revealed some networks that were similar for both stop success and stop fail. Given that the factor analysis groups regions that co-vary during the functional task, it is perhaps not surprising that similar anatomical coalitions should be observed for different cognitive processes. Notably, the function and relationship to phenotypes are quite different even for networks that share a similar anatomy. For example, the stop success basal ganglia factor was significantly different for the upper versus lower SSRT comparison ($P = 0.0131$), whereas the stop fail basal ganglia activation was not significant ($P = 0.957$). These observations suggest that it is the activity levels in these regions performing certain cognitive operations, and not the indiscriminant involvement of the regions, that relate to certain phenotypic differences. In addition, within a factor, the relative contribution of regions (that is, the factor loadings) differed between stop success and stop fail conditions, suggesting that the relative contributions of brain regions to specific networks are task specific.

The adolescent brain is highly plastic and its ongoing maturation can be disrupted by substance misuse[4,34]. However, disentangling cause and effect relationships between functional neural deficits and substance misuse is notoriously difficult in humans. We found that lateral orbitofrontal activity was reduced in those who misused any substance (alcohol, nicotine or illicit substances), even in those with only one to four lifetime uses of alcohol, which we contend strongly suggests a functional brain difference that preceded drug use. The orbitofrontal cortex (OFC) is often implicated in reduced impulse control and in drug-seeking behavior in humans[35] and nonhuman primates[36]. Human functional imaging studies suggest that the OFC is sensitive to drug-associated stimuli rather than to the specific drug itself[37], which may explain why the OFC effect is common to nicotine, alcohol and illegal substances. Adult cocaine addicts show decreased gray matter concentration in the OFC[38] and rats trained to self-administer amphetamine exhibit long-lasting decreases in OFC dendritic density[39], which indicates that OFC deficits can also arise from drug use.

In contrast with the reduction of OFC activity, activity in the right frontal network was increased for those participants who had used illicit substances. Animal models have shown that psychostimulant exposure increases dendritic spine density in the prefrontal cortex[40]. We found that users of illicit substances and non-users did not differ in SSRT; however, users of illicit substances required greater brain activity levels to produce a similar behavioral performance. Notably, when nicotine and alcohol use were controlled for, this increase in activity related to the number of lifetime uses, thereby supporting the notion that the right frontal network effects arise from the use of illicit substances[41]. Combining these effects with the preceding OFC effects leads to the following hypothesis: drug use risk related to compromised impulse control is characterized by relative hypoactivity in the OFC, whereas drug use effects related to compromised impulse control are characterized by relative hyperactivity in right PFC reflecting the increased difficulty that users experience when exercising inhibitory control.

Although previous neuroimaging findings have implicated the pre-SMA in inhibitory control, recent evidence[42] suggests that the pre-SMA has a dominant role in bridging the delay between expected reward and specific actions rather than determining whether an action is made. Our results bolster the concept of pre-SMA activity as a motivational signal for movement. Participants who had used both alcohol, nicotine and, for some participants, other illicit substances had increased activity in the stop success pre-SMA/PCG network.

Finally, we found that variation in the *SLC6A2* gene, which encodes NET, is related to activity in the stop success right frontal network. Drugs such as atomoxetine (a selective norepinephrine reuptake inhibitor) have been shown to improve response inhibition on SSTs in non-human animals, healthy volunteers and individuals with ADHD[43]. Moreover, atomoxetine was shown to enhance inhibition-related activity in the very same frontal brain regions in which we found genetic associations with *SLC6A2*. Our finding that the gene encoding NET is associated with the performance of the right frontal network therefore adds further evidence of a connection between inhibition, the specific role of norepinephrine and the function of the right frontal brain region.

Our results suggest that human adolescent impulsivity can be decomposed into a number of distinct networks and that these networks can be related to different phenotypes and to genetic variation in a gene encoding NET. The dissociation between different neural networks associated with subclinical ADHD and substance abuse is of potential clinical relevance, given the controversy that

exists concerning the relationship between ADHD and risk for substance abuse. Our data suggest that there is a degree of independence between these disorders and that an apparently common deficit in SSRT in ADHD and substance abuse may arise from different neurobiological pathways. Although it is important to identify these pathways for the insights that they might give into the development of different impulsive behaviors, it is equally important to note that early educational interventions focusing on improving cognitive control (including impulse control) have been shown to be effective in ameliorating cognitive control deficits[44]. The efficacy of these interventions may be related to the extent to which they engage the appropriate brain regions that underlie the impulsivity associated with specific disorders.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

H.G., T.W.R. and G.S. conceived the study. P.J.C., H.G., T.W.R. and R.W. designed the study. M.F.-B., H.G. and T.W.R. carried out the functional neuroimaging. G.J.B., C.B., P.J.C., H.F., J.G., H.G., A.H., B.I., E.L., K.M., J.-L.M, F.N., M.N.S., T.P., M.R., R.S., D.S., T.W.R., M.S. and A.S. acquired the data. J.-B.P., B.T. and R.W. carried out neuroimaging data processing and analysis. M.B., M.F.-B., E.C.L., M.S. and S.V.-K. analyzed behavioral data. M.A.B., T.D.R.C., M.L., A.L. and G.S. carried out genotyping and genetic analysis. R.W. and H.G. prepared the manuscript. M.A.B., P.J.C., T.B., T.P., T.W.R. and G.S. edited the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details accompany the online version of the paper.

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ONLINE METHODS

Standard operating procedures. The standard operating procedures for the IMAGEN project are available at http://www.imagen-europe.com/en/Publications_and_SOP.php and contain details on ethics, recruitment, neuropsychological tests, instructions for the SST (French, English and German), and for blood collection and storage.

Subjects. Data were acquired from 1,896 14-year-old adolescents. The recruitment procedures employed in the IMAGEN project have been described previously[45]. Individuals who provided assent, and whose parents provided informed written consent, completed an extensive battery of neuropsychological, clinical, personality and drug use assessments online and at the testing centers. Participants were excluded if, among other criteria, they had contra-indications for MRI (for example, metal implants, claustrophobia). The demographic information of the participants was: mean age = 14.55 ± 0.447 years, 51.7% female, 88.80% right-handed, verbal IQ = 110.67 ± 14.85, performance IQ = 107.57 ± 14.77.

SST. The SST required volunteers to respond to regularly presented visual go stimuli (arrows pointing left or right) and to withhold their motor response when the go stimulus was followed unpredictably by a stop signal (an arrow pointing upwards). Stopping difficulty was manipulated across trials by varying the delay between the onset of the go arrow and the stop arrow (stop-signal delay) using a previously described tracking algorithm[9]. A block contained 400 go trials and 80 variable-delay stop trials with between three and seven go trials between two stop trials. Stimulus duration in go trials was 1,000 ms and varied in stop trials (0–900 ms, 50-ms steps) in accordance with the tracking algorithm (initial delay = 250 ms).

fMRI acquisition. Full details of the MRI acquisition protocols and quality checks have been described previously, including an extensive period of standardization across MRI scanners[45]. Effect of MRI site was controlled by adding it as a nuisance covariate in all statistical analyses.

fMRI analysis. MRI data were processed using SPM8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/). Time series data were corrected for slice timing, then for movement, non-linearly warped onto MNI space using a custom EPI template, and Gaussian-smoothed at 5-mm full-width half maximum. Estimated movement (three translations, three rotations, three translations shifted one volume acquisition before and three translations shifted one volume acquisition later) parameters were added as nuisance variables. Each fMRI time series underwent automatic spike detection and any artifactual time points were regressed out of each subject's data.

Activation maps were computed using a general linear model with an autoregressive noise model. Based on behavioral records, each participant's design matrix included regressors for stop success trials, stop failure trials, trials on which the go response was too late, trials on which the go response was wrong (if any) and the nuisance variables. The regressors modeling the experimental conditions were convolved using SPM's default hemodynamic response function. A one-sample *t* test was conducted, testing activity on stop success trials (and separately on stop fail trials) against the implicit baseline of the go success condition, removing variance associated with the other regressors in the design matrix. ROIs were generated using WFU Pickatlas[46] and associated anatomical atlases[47,48], and the mean contrast value for each ROI was calculated for each subject for both stop fail and stop success.

Statistical analysis: factor analysis. The exploratory factor analysis was completed using Predictive Analytics Software (SPSS) version 20. We chose to use exploratory factor analysis because we wished to explore the possible underlying factor structure of a set of observed variables without imposing a preconceived structure on the outcome. The goal of the factor analysis was to reduce the number of ROIs to a smaller number of factors (see **Supplementary Table 13** for the list of initial ROIs), following published recommendations[49]. Our factor analysis was conducted according to the criteria that the factors must have item loadings of 0.5 or greater, a minimum communality of 0.4 (all ROIs had a communality over 0.4 following extraction), and that item loadings should not be above 0.33 on two or more factors.

The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.857 (0.5 is considered the minimum value for a sample to be adequate). Bartlett's test of sphericity was significant ($\chi^2(465) = 37{,}146.142$, $P < 0.001$), indicating that there was an underlying correlation structure and that a factor analysis was appropriate.

Initially, the factor analysis was conducted on a sample of 1,252 adolescents (66% of the final sample, these data were available as a first cohort prior to the addition of the remainder of the sample). The factor analysis with the initial 66% of the final sample revealed a seven-factor solution containing 31 regions for the stop success contrast and a six-factor solution containing 28 regions for the stop fail contrast. With the constraint that a seven-factor solution be found, 50 repetitions of the factor analysis with randomly selected subsets of 50% of the sample produced identical factors for the stop success contrasts and the same six-factor solution was found for 49 of 50 repetitions of the factor analysis for the stop fail contrast. To further test the replicability of this solution, a separate factor analysis was subsequently conducted with an entirely new set of data (33% of the final sample), which was conducted according to the same protocol for the initial factor analysis (that is, without an a priori restriction on the number of factors) and found the same seven-factor solution (31 regions) for the stop success contrast and the six-factor solution (28 regions) for the stop fail contrast. The factor analysis was therefore re-run with both samples combined. Factor scores were calculated using a regression method that weighted each participant's ROI score according to the factor loading matrix (scores have a mean of zero). As a further control, any factor scores over three standard deviations from the mean score of that factor were excluded from any subsequent statistical test.

SSRT analysis. Subjects were excluded from the SSRT analysis if they had more than 80 errors on the go trials (responses incorrect or too late). If the subject responded prior to a stop stimulus (stop too early, STE), then that stop trial was repeated (a maximum of seven such trials were repeated). This procedure may have affected the accuracy of the SSRT calculation as participants varied in their number of STE trials; given the limit of just seven repetitions, participants varied in the number of STOP trials available for the calculation of the SSRT. Thus, for subjects with more than eight STEs, we calculated the SSRT up to the point of the eighth STE. For some subjects, however, this occurred early in their run. Thus, we restricted the SSRT analysis only to subjects who did not reach their eighth STE before their 300th trial. The SSRT can be computed by various methods (see ref. 50 for a review), with the assumption that successful stop trials are those in which, had those trials been go trials, the reaction times would have come from the slower tail of the population of reaction times, whereas the reaction times recorded on unsuccessful stop trials are drawn from the faster tail of the distribution. We computed the SSRT by taking the Go RT at the percentile corresponding to the proportion of unsuccessfully inhibited stop trials and subtracting the mean stop-signal delay.

Development and well-being assessment (DAWBA) interview. The DAWBA interview (see http://www.dawba.info/) was administered at the research site, using a combination of parent and adolescent interviews and rating techniques to generate psychiatric diagnoses based on the Diagnostic Statistical Manual of Mental Disorders[51], Version 4 (American Psychological Association, 1994) for ADHD[52]. The generated band ranges from level 0 up to level 5, corresponding to the approximate prevalence rates in an epidemiological sample for the disorder in question (range = 0.1–70%)[53].

We identified 171 participants with subclinical ADHD symptoms (defined as a score greater than 2 on the DAWBA interview, mean score = 2.58 ± 0.72) and matched each of them with a control participant (ADHD = 0) from the same site and of the same sex, obsessive-compulsive disorder score, handedness, and of similar age and IQ. The mean age for the ADHD group was 14.53 ± 0.38 years and the mean age of the control group was 14.53 ± 0.39 years. The mean verbal IQ for the ADHD group was 107.29 ± 15.69 and the mean verbal IQ of the control group was 110.15 ± 13.18. The mean performance IQ for the ADHD group was 102.53 ± 14.83 and the mean performance IQ of the control group was 105.44 ± 14.35. Participants were matched, as closely as possible, with a participant with a similar score on alcohol, cigarette and illegal substance use.

European school survey project on alcohol and other drugs (ESPAD). Subsections of the ESPAD[54] items were used, including quantity (number of drinks on a typical day when drinking) and frequency (number of lifetime occasions, seven response options from 0 to 40 or more) of alcohol use and severity of lifetime illicit drug use.

Intelligence quotient. The Wechsler intelligence scale for children was used to measure IQ and was administered by an experimenter in the study center. The vocabulary and similarities subscales were employed to determine verbal IQ. The block design, matrix reasoning and digit span subscales were employed to determine non-verbal/performance IQ. Data were normed according to the subject's age.

Genetics. We investigated 192 SNPs, which were selected from each member of the full set of autosomal catecholamine genes; namely, those that are directly involved in the synthesis, degradation, transport and receptor signaling of dopamine and/or norepinephrine (see **Supplementary Table 11** for the full list of genes and SNPs investigated). We tested for association between these genetic markers in those participants for whom we had previously found a relationship between activation and SSRT in the stop success right frontal, stop success basal ganglia and stop fail bilateral frontal networks.

Imaging and genetic data for any participant were only included in analyses when that individual also had an SSRT value within three standard deviations of the mean[31] (n = 820). Correlations were calculated between the functional imaging variables and potential covariates (verbal IQ, performance IQ, gender, age, testing site and handedness). As handedness was not significantly correlated with any of the imaging variables, it was not included as a covariate. The permutation analysis described below was then performed separately for each imaging variable using Matlab (v.2008a).

For each SNP, an association analysis between the imaging variable and genotype was performed using a single-step additive regression model that included the nuisance covariates. The absolute (unstandardized) beta value for the imaging variable was recorded (these values are hereafter referred to as the original (unshuffled) test statistics) and was followed by a single step permutation method in which each individual's index (the profile that is made up of their score on the imaging variable and their covariate scores) was shuffled multiple times relative to the genetic data. Notably, both the linkage disequilibrium structure between the SNPs and the correlation structure between the imaging variable and the covariates were maintained. The randomization of only the association between each individual's profile and each individual's SNP set effectively deals with missing data and allows for correction for multiple related comparisons by comparing the original test statistic for any SNP to a maximal distribution over all SNPs[55]. For each shuffled configuration of the data, an additive association analysis (as described above) was performed for every SNP and the maximal absolute value observed for the test statistic (beta) of the imaging variable across all SNPs was recorded. This process was repeated 100,000 times and a list of the maximal beta values (one beta value per shuffle) was generated. The single-step permuted P value for any given marker was then calculated as the fraction of maximal beta values that were greater than or equal to the absolute value of the original (unshuffled) test statistic for the marker in question.

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