



Review

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Genetics of impulsive behaviour

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Impulsivity, defined as the tendency to act without foresight, comprises a multitude of constructs and is associated with a variety of psychiatric disorders. Dissecting different aspects of impulsive behaviour and relating these to specific neurobiological circuits would improve our understanding of the etiology of complex behaviours for which impulsivity is key, and advance genetic studies in this behavioural domain. In this review, we will discuss the heritability of some impulsivity constructs and their possible use as endophenotypes (heritable, disease-associated intermediate phenotypes). Several functional genetic variants associated with impulsive behaviour have been identified by the candidate gene approach and re-sequencing, and whole genome strategies can be implemented for discovery of novel rare and common alleles influencing impulsivity. Via deep sequencing an uncommon *HTR2B* stop codon, common in one population, was discovered, with implications for understanding impulsive behaviour in both humans and rodents and for future gene discovery.

1. Impulsivity

Impulsivity is the tendency to act without foresight. It has been associated with many psychiatric disorders, including addictions, attention deficit/hyperactivity disorder (ADHD), bipolar disorder and personality disorders such as borderline personality disorder (BPD) and antisocial personality disorder (ASPD). The fourth edition of the *Diagnostic and Statistical Manual* (text revision) also identifies a group of psychiatric illnesses that are collectively defined as impulse control disorders not elsewhere classified. These include intermittent explosive disorder (IED), pyromania, kleptomania, pathological gambling and trichotillomania. Finally, impulsivity is associated with suicidal behaviour, aggressiveness and with certain forms of criminality.

Impulsive behaviour is not always maladaptive and is advantageous in situations in which it is important to respond rapidly and to take advantage of unexpected opportunities.

As with many behavioural constructs, impulsivity is multifaceted and encompasses behaviour due to inadequately sampled sensory evidence (attentional impulsivity), failure of motor inhibition (impulsive action), the tendency to accept small immediate rewards versus large delayed or unlikely ones (impulsive choice or non-planning impulsivity) and risky behaviour in the context of decision-making [1]. Impulsivity may also be expressed in various forms, including aggression. This rich variety of modes of expression suggests that impulsivity is not a unitary construct. Defining different forms of impulsivity could advance understanding of the neurobiological basis of diseases for which impulsivity is a component (figure 1).

2. Measurement

Constructs of impulsivity ultimately depend on measures, and reciprocally, measures of impulsivity have been developed to assess certain constructs. There are a variety of distinct measures of impulsivity which may access different components of psychobiology, and these measures also have analogues in animal behavioural models (for a review, see [2,3]).

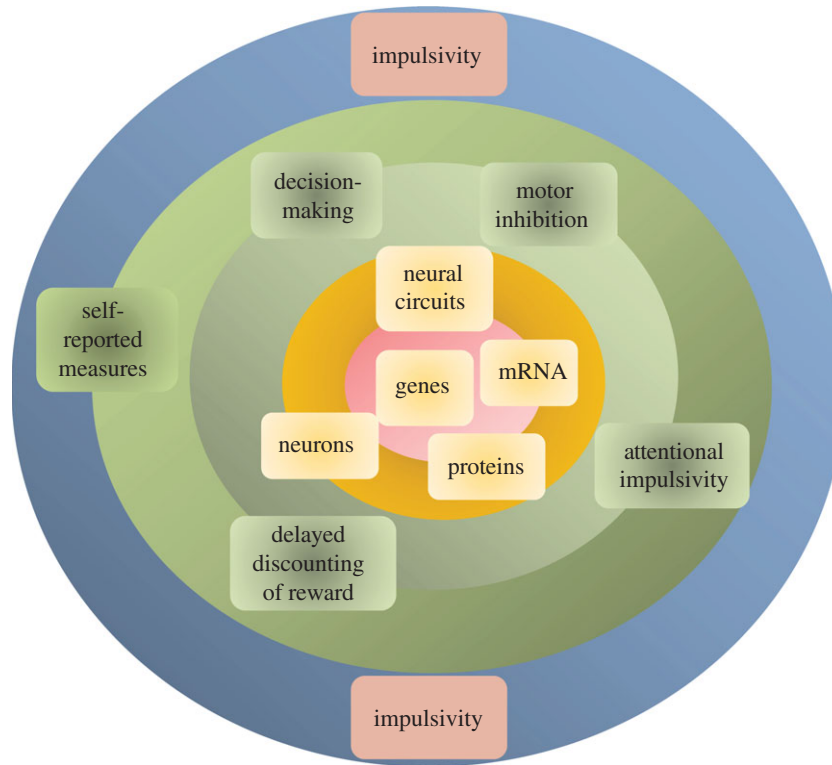


Figure 1. Impulsivity is a heritable, disease-associated trait, which may be useful as an endophenotype for gene discovery. However, impulsivity is not a unitary construct but is itself a complex trait. Multiple laboratory behavioural tasks and self-report measures are used to assess aspects of impulsivity. Different neural circuits and genes, with pleiotropic effects on behaviour, modulate impulsivity. Different colours are to indicate the progression from genes to disease.

3. Delayed (or delay) discounting of reward: impulsive choice

An example of impulsive choice occurs when an individual, or animal, preferentially chooses an immediately available small reward rather than enduring delay for a larger one [4,5]. The human and the animal delayed discounting paradigm may be comparable in that they both measure the discounting of reward against a temporal delay. In humans, many versions of this paradigm have been tested [6–8] in which individuals experience actual delays, however, in tests such as the Kirby test [9] the delay is not actually experienced and is replaced by an imaginary time interval: e.g. *would you prefer 33 dollars today or 80 dollars after 14 days?* There are several important caveats in interpreting delayed discounting. It has been observed that lower socioeconomic status (SES) of their families predicts the tendency of adolescents to place higher value on immediate reward [6], and SES has therefore been used as a covariate. In certain situations, it may be safer to place a higher value on immediate reward rather than the larger, uncertain reward, which may actually represent a gamble against future unpredictable events. The valuation of immediate reward is also influenced by immediate need. However, when it has been applied in appropriate contexts, delayed discounting has been observed to relate with other measures of impulsivity. For example, de Wit *et al.* [10] found that in humans preference for immediate rewards was positively correlated with the non-planning impulsiveness subscale of the Barratt Impulsiveness Scale (BIS) [11]. Individuals with a high rate of delayed discounting tend to discount longer-term consequences of their decisions and actions, and their behaviour is largely driven by the prospect of immediate gratification rather than the pursuit of

long-term goals. Individual differences in delayed discounting of reward have been associated with addiction [12,13], and animal studies have shown an association between reward discounting and alcohol preference and rates of cocaine self-administration [13,14].

The neurobiological bases of delayed discounting implicate the core of the nucleus accumbens (NAcc). Excitotoxic lesions of the NAcc core determine a shift towards immediate small rewards [15]. This subregion of the NAcc is part of a larger network, including the amygdala and the prefrontal cortex (PFC). In the orbitofrontal cortex (OFC), an increased release of dopamine has been observed during the choice phase of the delayed discounting task [16]. Choice of a monetary reward or juice or water is associated with an increase in activity of the ventral striatum and the medial PFC (mPFC) [17], while in contrast the choice for a delayed option was associated with higher activity in the lateral PFC and OFC [18].

4. Decision-making

Delayed discounting may contribute to the performance on complex behavioural tasks to assess risky decision-making. In the human, risky decision-making has been investigated using the Balloon Analogue Risk Task (BART) [19] and the Iowa Gambling task (IGT) [20]. During the BART, subjects earn money by inflating a balloon displayed on a computer screen. At every mouse click, the balloon inflates and money is gained, until the balloon pops and all the savings are lost. The subject can stop inflating the balloon at any time and save the money gained. BART measures, including numbers of popped balloons and mouse clicks, correlate with

drug use [21] and with sensation seeking and impulsivity measured with the BIS or the Eysenck impulsiveness scale [19,22,23]. Other studies though failed to replicate the association with the BIS [24].

The IGT involves choices between larger money gains associated with higher risk versus lower gains that over time are more advantageous. The OFC, mPFC, amygdala and anterior cingulate cortex are implicated in decision-making during the IGT [25,26]. Similar regional activations have been described for the BART [27]. As previously discussed, most animal models of risky decision-making deal with the failure to win any additional gain (e.g. smaller but certain reward versus larger but uncertain reward). Zeeb *et al.* [28] have conceptualized a novel rat gambling task, in part based on the IGT, where animals 'play the odds' and chose between multiple outcomes based on both the size of the expected reward and the probability and magnitude of expected punishment, which consists of time-out periods during which rats cannot earn reward. It is however to be remembered that food rewards are used in these tasks, and the animal will always record a positive gain by the end of the task. This model has been used to analyse the effect of both serotonergic and dopaminergic agents and to study the biological basis of gambling.

5. Motor inhibition: action cancellation

The Stop Signal Reaction Time task (SSRT) [29] measures the ability to exert volitional control over a response that has already been initiated rather than choice selection. It comprises a primary go cue and a secondary stop cue. Generally, the go cue is a visual stimulus, which prompts subjects to give a response, but on a proportion of the trials the subject receives an auditory stop signal that indicates that the subject has to cancel responding to the cue. The stop signal occurs after different delays following the primary go cue. It is much more difficult for the subjects to cancel the response as the delay increases. Longer stop signal reaction times are positively associated with higher scores on the impulsivity subscale of the Eysenck Personality Inventory [30]. ADHD is characterized by poor behavioural control and children with ADHD showed impairment on this task [31]. Their symptoms were reversed by the use of methylphenidate, a psychomotor stimulant used in the treatment of ADHD [31].

The Go/No go is a classic neuropsychological task in which the subject has to respond to correct stimuli (go) and withhold response to incorrect stimuli (no go) [32]. The Go/No go and SSRT tasks are similar in that they measure inhibition of a prepotent response, but differ in that the Go/No go task requires subjects to execute or inhibit a response and the SSRT task requires subjects to inhibit a response they have already initiated. No significant correlation is described between the BIS and the Eysenck impulsiveness scale and the behavioural performance on the Go/No go task [33,34].

Some studies [35] describe a correlation between these tasks, while other studies do not find a significant correlation between the two [36], suggesting that they may be assessing different aspects of impulsivity.

Classically, the PFC has been implicated in Go/No go responding and the OFC has been related to disinhibition

[37]. The role of the right inferior frontal gyrus (RIFG), associated with impulsive behaviour in healthy subjects and ADHD [38] is controversial [39,40].

6. Premature responding on the 5-choice serial reaction time task: attentional impulsivity

The 5-choice serial reaction time task (5CSRTT) measures impulsivity in the context of general attentional capacity in rodents [41]. The 5CSRTT was based on the Continuous Performance Test (CPT) used for measuring sustained attention in humans [42]. In the CPT, participants view characters displayed on a computer screen and respond when the characters match a target stimulus. Errors occur when the subject responds positively even though sequences do not match perfectly. The error occurs when the subject responds prematurely before processing the full sequence. CPT performance has been linked to BIS scores [43,44] and to the number of diagnostic ADHD symptoms [45]. The 5CSRTT requires the rodent to respond to a visual stimulus presented in one of five locations. The rodent has to respond to the correct location in order to earn food reward. Premature responses indicate the rodent's inability to wait for the correct stimulus and are thought to be analogous to errors made on the CPT. Lesions of the NAcc core contribute to premature responses in the 5CSRTT [46].

7. Self-reported impulsivity in humans

In humans, impulsivity may be assessed by self-report questionnaires, for example, the Barratt Impulsivity Scale (BIS-11) [47], the UPPS-P Impulsive Behaviour Scale (IBS) [48], the Impulsivity Rating Scale [49], the Karolinska Scale of Personality impulsivity subscale [50], the Eysenck Personality Questionnaire (EPQ) [23], the Temperament and Character Inventory (TCI) [51], the Multidimensional Personality Questionnaire (MPQ) [52] and the Buss Durkee Hostility Inventory ([53] see [1] for review). These self-report measures, as previously described, often fail to correlate with experimental measures suggesting either that they are assessing different aspects of impulsivity or perhaps a difference in accuracy. Self-report scales are more reflective of the subjective view that an individual has of his own behaviour; however, some progress has also been made in relating such measures to differences in brain function. As described earlier, no association was found between the BIS and the impulsivity subscale of the EPQ with the Go/No go task in healthy individuals [34]. Despite this negative finding, significant associations were identified between high impulsivity scores on the EPQ and the BIS and activation of paralimbic areas, including the RIFG and right insula, and the left superior temporal gyrus, respectively [34]. This study reveals a lack of correlation between different measures of impulsivity but also shows how different self-report questionnaires may address different aspects of behaviour and produce different results when associated with brain activation during behavioural inhibition. Similarly, the BIS did not show correlation with performance data on the Go/No go task, but a negative correlation was observed between the motor impulsiveness of BIS and No go-related activation in the right dorsolateral PFC [54]. Impulsivity, measured with the BIS, correlated positively with bilateral ventral amygdala,

dorsal anterior cingulate and caudate activations, and inversely with activity in the bilateral ventral PFC and right dorsal amygdala in healthy subjects [55].

Sripada *et al.* [56] observed that trait impulsivity measured with the BIS moderates activity in the mPFC in the contest of a delayed discounting task, consistent with previous studies that describe activation of the mPFC during decision-making [57,58]. A study by Lee *et al.* [59] explored the association between scores on the BIS and striatal D2/D3 receptor availability assessed by positron emission tomography in both healthy controls and methamphetamine-dependent individuals. A negative association between D2/D3 receptor availability and impulsivity was detected in the group of addicts, consistent with the role of these dopamine receptors in impulsivity.

For the purpose of gene discovery and candidate gene studies, behaviourally measured aggression has previously shown a strong relationship with biological predictors. Aggression can be instrumental, purposeful and goal oriented, or defined as reactive or impulsive [60,61]. ASPD, BPD or IED are disorders that share genetic risk for impulsive aggression [62]. The Brown-Goodwin Lifetime History of Aggression (BGHA) instrument [63] is an 11-item questionnaire that assesses lifetime aggressive behaviour by counting the number of times each type of aggressive behaviour occurred. Episodes measured include temper tantrums, and violence against self, property and others (including authority) in various social contexts, including family, school and work. BGHA aggression is predicted by higher testosterone in men [64] and also has been related to functional variation of the *MAOA* gene. The *MAOA* gene was observed to interact with testosterone levels to predict aggressive behaviour measured with the BGHA [65], and *FKBP5*, which encodes a protein involved in cortisol response, interacts with stress exposure to predict BGHA scores [66].

8. Heritability of impulsivity

Impulsivity is moderately heritable [67] as are disorders with which it is associated [62,68]. The heritability of self-reported measures of impulsivity from the Karolinska and the control scale of the MPQ questionnaire is approximately 45 per cent [69,70]. Impulsivity-related measures from the revised form of the EPQ and the TCI are approximately 50 per cent heritable [71,72]. Impulsivity, measured with the BIS-11, but not sensation seeking, was significantly elevated in siblings of stimulant abusers compared with controls [73].

Concerning behavioural measures of impulsivity, the heritability of responses on the delayed discounting task was evaluated in a longitudinal twin study [6]. Heritability increased from 30 to 51 per cent from age 12 to 14 suggesting an increasing role of genetic influence with age. In the same cohort, BART measures predicted risk-taking during the passage from early to mid adolescence, vulnerability to substance abuse, accidents and violence increasing rapidly during this interval [74]. There appeared to be a major gender difference. At age 12, heritability of risk-taking was modest but significant in both sexes; at age 14, heritability of risk-taking increased from 28 to 55 per cent in males but went from 17 per cent to non-significant in females.

Animal models would seem to be ideally suited to measure the heritability of impulsivity. Impulsivity does

appear to correlate with heritable variation in serotonin metabolism in the rhesus macaque [75], as it also does in humans [76]. Rodent genetic studies have frequently focused on related phenotypes, such as aggression. The *Htr2b* gene-knockout impaired delayed discounting and led to increased novelty seeking, illustrating the potential for rodent models to explore genetic effects on impulsivity [77].

9. Genes influencing impulsivity

Pharmacobehavioural studies have implicated several neurotransmitters in impulsivity, and several genes associated with impulsivity alter function of these neurotransmitters.

Dopamine- and serotonin-releasing neurons are prominent in brain regions that regulate impulse control. Dysregulated activity of the monoamine neurotransmitters has been demonstrated to be involved in impulsivity in neuropharmacological, gene knockout and genetic association studies. The genes discussed here alter monoamine neurotransmitters function, have been associated with impulsivity/aggression and have in some cases been tested for association with responses to laboratory behavioural tasks probing impulsivity in humans (table 1).

Serotonin is the molecule that has been most consistently associated with impulsivity, in particular as manifested as impulsive aggression and suicide. Serotonin was associated with aggression and impulsivity by neurochemical and neurobehavioural studies in humans and in animal models [87–89]. Linnoila and colleagues examined serotonergic biomarkers in violent offenders and alcoholics. They found that cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) was reduced only in individuals whose aggressive behaviour and violence was impulsive rather than those in whom it was premeditated. In rodent models, manipulations that lower 5-HT signalling increase impulsivity and aggression [87], while increasing 5-HT activity with 5-HT precursors, 5-HT reuptake inhibitors or 5-HT1A and 5-HT1B receptor agonists can reduce aggressive behaviour in rodents [87,90].

The tryptophan hydroxylase 2 (*TPH2*) gene encodes for the enzyme which catalyses the rate-limiting step for brain serotonin biosynthesis, and a *TPH2* haplotype predicts decreased CSF levels of the serotonin metabolite 5-HIAA and suicide attempt [91].

The *MAOA* gene, encoding monoamine-oxidase A, an enzyme that metabolizes monoamine neurotransmitters, has been shown to play a role in modulating aggression: Brunner *et al.* [92] discovered an *MAOA* stop codon (C936T) that produces complete deficiency of *MAOA* activity in hemizygous males and co-segregates with severe impulsivity in one Dutch family. It has also been observed that *MAOA* knockout mice have higher levels of monoamines and increased aggressive behaviour [93]. A functional variable number tandem repeat in the *MAOA* regulatory region (*MAOA-LPR*) has been identified with increased enzyme expression for the carriers of the 3.5–4 repeat alleles (high expression, H, alleles) and lower expression for the 2, 3 and 5 alleles carriers (low expression, L, alleles). The *MAOA-L* allele modulates the effect of childhood adverse events increasing vulnerability to develop antisocial behaviour in adulthood [94,95].

Individual differences in serotonin 1A receptor binding have been associated with lifetime aggression [96]. A functional *HTR1A* single-nucleotide polymorphism (SNP, rs6295) was associated with both BIS and EPQ scores in a population

Table 1. Examples of genes associated with laboratory behavioural tasks assessing impulsivity in humans. HV, healthy volunteers.

gene	references	sample <i>n</i>	locus	impulsive choice (delayed discounting)	decision-making (BART, IGT, other gambling tasks)	motor inhibition (SSRT, Go/No go)	attentional impulsivity (CPT)
<i>5HT1A</i>	[78]	<i>n</i> = 69, HV	rs6295 C/G		no association		
<i>TPH2</i>	[78]	<i>n</i> = 69, HV	functional haplotypes		low expression haplotype < risky decisions		
	[79]	<i>n</i> = 168, suicide attempters	rs118997 C/T		no association		
	[80]	<i>n</i> = 199, HV	rs1386483 T/C			TT genotype > SSRT	
<i>SLC6A4</i>	[78]	<i>n</i> = 69, HV	HTTLPR-S/L		no association		
	[81]	<i>n</i> = 52, HV	HTTLPR-S/L				SS > LS > LL impulsivity
	[82]	<i>n</i> = 28, HV					
		<i>n</i> = 66, ecstasy abusers	HTTLPR-S/L		LL > LS > SS impulsivity		
		<i>n</i> = 30, polydrug users					
	[83]	<i>n</i> = 127, HV	HTTLPR-S/L		no association		no association
	[84]	<i>n</i> = 328, ADHD	HTTLPR-S/L	S carriers > impulsivity			
		<i>n</i> = 131, healthy siblings					
<i>MAOA</i>	[79]	<i>n</i> = 168, suicide attempters	LPR-H/L		no association		
<i>SLC6A3</i>	[85]	<i>n</i> = 405, HV	rs37020 G/T			G allele > impulsivity	
	[84]	<i>n</i> = 328 ADHD, <i>n</i> = 131 healthy siblings	rs460000 A/C			C allele > impulsivity	
		<i>n</i> = 328 ADHD, <i>n</i> = 131 healthy siblings	VNTR	no association			
	[86]	<i>n</i> = 36, ADHD	VNTR	10/6 allele > impulsivity			
		<i>n</i> = 32, HV					
<i>DRD4</i>	[86]	<i>n</i> = 36, ADHD	VNTR	no association			
		<i>n</i> = 32, HV					

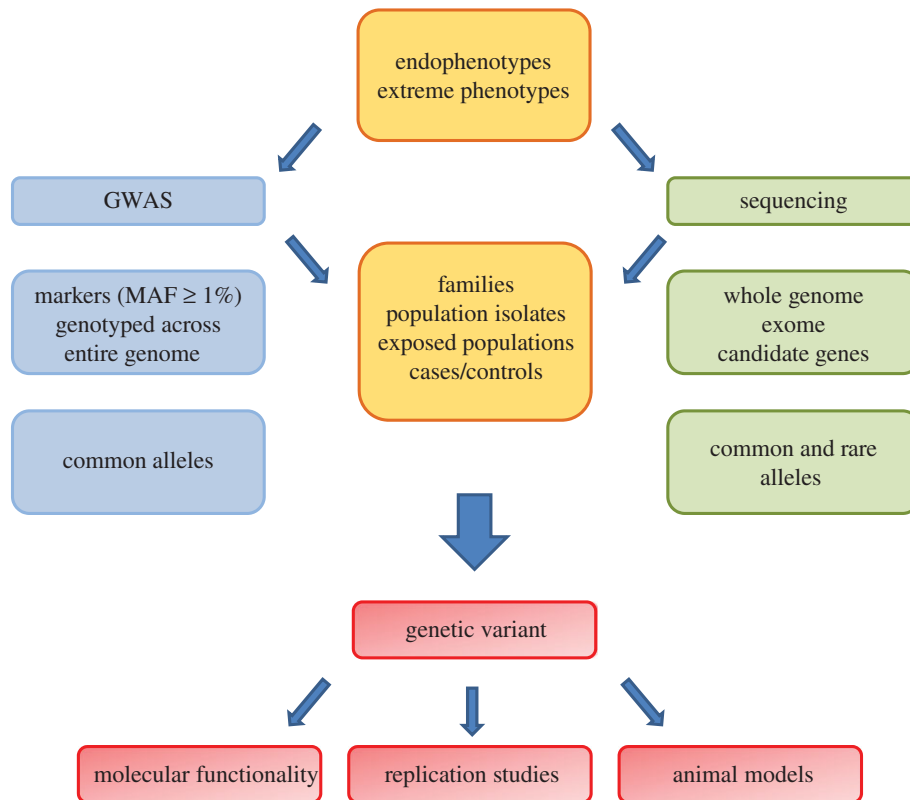


Figure 2. For complex traits such as impulsivity, the power of both genome-wide association studies (GWAS) and deep sequencing may be enhanced via studies of endophenotypes, extreme phenotypes, exposed populations and founder/family cohorts. Validation of findings is a multilevel problem that includes confirmation of molecular function, replication and extension to interventional experimental models, including animal models.

sample [97]. The serotonin receptor 1B gene (*HTR1B*) is located with several mouse alcohol QTLs on chromosome 9, and gene-knockout studies performed in mice implicated the *HTR1B* gene in both alcohol preference and aggression [98,99]. In humans, a non-synonymous mutation (Gly861Cys) in the *HTR1B* gene was linked to antisocial alcoholism in two independent populations, including a Finnish violent offenders cohort [100].

Many pharmacological studies with serotonin 2A, 2B and 2C antagonists and agonists have implicated these receptors in impulsive behaviour [101]. Two subunits of serotonin type 3 receptors, 3A and 3B, have so far been identified; variation within the *HTR3B* gene was associated with alcohol use disorder in comorbidity with ASPD [102].

A common polymorphism (HTTLPR) is located upstream of the serotonin transporter gene (*SLC6A4*): a 14-repeat allele (S) reduces transcriptional efficiency compared with the 16 repeat allele (L) or the L allele containing a G substitution [103]. Stress-modified associations have been reported also for this polymorphism to suicidality [104,105], and *HTTLPR* was associated with trait impulsivity measured with the BIS [106].

Dopamine regulates cognitive function, attention and responses to reward, all of which are factors in impulsivity. Decreased levels of D2 receptor in the NAcc predict spontaneous impulsivity in rats [107]. Variation in the dopamine transporter gene (*SLC6A3*) has been shown to moderate risk for ADHD, which is characterized by both hyperactivity and impulsivity [86,108]. The dopamine transporter is also the target of stimulant compounds such as methylphenidate, which reduces symptoms of behavioural disinhibition in ADHD and also improves the performance to the SSRT in healthy individuals and adults with ADHD [109,110]. There

is also evidence of an association between increased risk of ADHD and variation in the dopamine D4 receptor gene [108]. However, a recent genome-wide association study (GWAS) of ADHD [111] revealed no locus significant at the genome-wide level. This study may have been stymied by etiologic and genetic heterogeneity, or by rare alleles and short tandem repeat (STR) alleles whose effects are poorly detected by GWAS.

As illustrated by multivalent effects of polymorphisms, such as *COMT* Val158Met, which has countervailing effects of executive cognitive function [112] and anxiety/stress response [113] and pain [113,114] probably both mediated by alteration of levels of dopamine and other monoamine neurotransmitters, most genes that alter brain function affect the function of multiple circuits and may have effects elsewhere in the body, a phenomenon known as *pleiotropy*.

10. Methodologies for gene discovery

The ability to scan the entire genome with genotyping arrays and massively parallel sequencing opened the era of genome-wide analyses, enabling hypothesis-free identification of loci influencing diseases and other phenotypes (figure 2). The rationale underlying genome-wide association (GWA) is the common disease–common variant hypothesis, which posits that common complex diseases are attributable to abundant (greater than 1–5%) alleles of small or moderate effect. Under epistatic models, effects are non-additive—unique combinations of alleles at different loci lead to the phenotype. Based on ratios of trait concordances between individuals at different degrees of relationship, the

inheritance of various psychiatric diseases appears to be predominantly additive—for example, see Goldman *et al.* [115] reviewing the MZ:DZ ratios for ten different addictive disorders.

GWA is a hypothesis-free search strategy employed to detect effects of relatively common alleles. Via GWA, more than 500 independent SNP associations ($p < 1 \times 10^{-8}$) to diseases and other phenotypes have been identified ([116], National Human Genome Research Institute Catalogue of Published Genome-Wide Association Studies, <http://www.genome.gov/gwastudies/>). These associations primarily involve small effect sizes (e.g. disease odds ratios less than 1.3), the functional loci responsible for the associations have usually not been identified, and most of the genetic variance has remained unexplained [117–119]. For example, height is a highly heritable trait (80–90%) for which GWA has been conducted in samples of up to 30 000 subjects [120], but the common variants that have been identified explain 3.7 per cent of population variation in height. Likewise, in a discovery sample size of 10 128 and a replication sample of 53 975, 18 common variants associated with type 2 diabetes appear to explain about 6 per cent of the increased risk of disease among relatives [121]. A GWA on temperament (TCI), a trait with heritability estimates that range between 30 and 60 per cent, was undertaken in an Australian sample of 5117 subjects but no statistically significant loci were detected [122]. A GWAS of five broad dimensions of personality (Revised NEO Personality Inventory—exploring neuroticism, extraversion, openness to experience, agreeableness and conscientiousness—[123]) was conducted on approximately 4000 subjects from Sardinia, a population isolate. The few loci identified, at sub-threshold significance, explained less than 1 per cent of the variance and failed to replicate in an independent follow-up sample [124]. It is likely that increasing the sample size will lead to the identification of additional genes influencing phenotypes such as these, but the question is how many, and how much of the heritable trait variance. As sample size is increased, various types of heterogeneity, including consistency of phenotyping, ascertainment, environmental exposure and genetic background, are likely to detract from power.

Several suggestions have been made to explain the missing heritability in GWA studies. The phenotypes and sampling frameworks in the GWA studies may not be equivalent to ones used in the heritability studies, although in some instances, for example, the GWA of temperament in the Australian Twin study [6,122], the context was the same. The effects of variants may be context-dependent, leading to failures to detect loci in the absence of exposure, or in the presence of exposures that overwhelm the effects of genes [125]. The use of intermediate phenotypes that are less subject to environmental perturbation and closer to the function of molecular networks appears to amplify power of GWA [126]. If, despite the lack of evidence from transmission studies, ‘epistasis is the rule’, it may be necessary to test combinations of common alleles [127]. It is also possible that parental-origin-specific associations may be important [128]. Finally, there may be a high amount of genetic heterogeneity. Rare variants and alleles which are common only in particular populations confer a substantial portion of the risk for medical genetic diseases. For example, in cystic fibrosis (*CFTR*) and breast cancer (*BRCA1*, *BRCA2*) hundreds of rare disease-causing variants have been identified in addition

to certain variants that are common in particular populations [129,130]. The 1000 Genomes Project is now extending the catalogue of the known common variants to ones with a frequency of approximately 1 per cent (<http://www.1000genomes.org/>). Inclusion of these less common polymorphisms in genotyping arrays will enable identification of new associations.

However, to capture rare variants, it will be necessary to sequence target regions, exomes and genomes of cases, rather than only genotyping catalogues of known variants. Such ‘deep sequencing’ is enabled by next-generation sequencers. Cost and workflow of massively parallel sequencing is rapidly improving. Proof-of-concept studies involving identification of variants causing rare Mendelian diseases have been successful using both the whole genome and exome sequencing approaches. Ng *et al.* [131] identified the causal gene for Freeman-Sheldon syndrome by exome sequencing four unrelated cases and eight controls. The cause of this disorder was previously known but the authors proved that by exome sequencing it was possible to reliably identify the causal gene, *MYH3*. *MYH3* was implicated in all four of the cases, by an indel, non-synonymous variant, and a splice site variant, and in none of the controls. Via exome sequencing, the cause of another rare Mendelian disease was identified. Ng *et al.* [132] sequenced the exomes of four cases (in three independent kindreds) and eight controls and uncovered the cause of Miller syndrome, *DHODH*, by identifying genes containing non-synonymous variants, splice site variants and coding indels present in cases but not in controls.

It is more difficult to identify genes for complex disorders by deep sequencing, but several strategies make it feasible to overcome the main problem, which is that the rarity of variants makes it difficult to establish causality. By sequencing phenotypically extreme individuals, a larger sample of rare functional variants can be more efficiently accumulated. A variant of large effect at low frequency may be enriched in frequency in such a sample. However, many rare, disease-causing variants are specific to families or populations. By sequencing family trios, it is possible to identify *de novo* variants, as illustrated by the sequencing of probands and parents of individuals with unexplained mental retardation and sporadic autism [133,134]. For the majority of disease-causing variants which are not *de novo*, as shown by heritability studies, the study of extended families and founder populations leads to observation of multiple instantiations of the same genotype. For example, in the first degree relative of an individual with a rare autosomal dominant allele the frequency of the allele is approximately 25 per cent, and approximately 50 per cent of the first degree relatives are carriers. The genetic heterogeneity of medical genetic diseases is greatly reduced in founder populations, as will be discussed. For family-focused sequencing, ones with multiple affected individuals can be selected, the model being the type of analyses performed for rare Mendelian diseases, such as Miller syndrome. Distantly related individuals may also be sequenced, the goal being to filter the variants that could potentially be responsible for the trait. However, the abundance of the complex disease phenotypes presents a serious obstacle. The ‘same’ phenotype in distantly related, and even closely related, relatives may be attributable to the influence of different genes. An important test is the cosegregation of variant with phenotype in the same family.

This testing is essentially a meiotic linkage test. Therefore, if the family was previously tested for meiotic linkage with a panel of STR or SNP markers and did not in the first place generate a significant meiotic linkage signal, it is unlikely that the role of a variant found by deep sequencing can be established by a statistical test within the family. It is important to recognize that non-statistical validating methods are usually available. These include the detection of biochemical or physiological correlates, validation in appropriate animal models, responses to pharmacologic or endocrine challenge, and the discovery of other functional variants at the same gene or functionally related genes in other families or populations of affected individuals.

The enormous number of variants generated by sequencing has to be selected on the basis of potential functionality, as is the case for deletions, duplications, premature stop codons and non-conservative amino acid substitutions. It is important to recognize that in addition to variants that may more subtly alter gene expression and function, other variants that contribute to common complex disorders may be more obviously functional.

11. *HTR2B*

To detect a rare stop codon contributing to a complex behaviour, namely impulsivity, we integrated several of the strategies just described [77]. These included sequencing of a limited panel of genes, thus minimizing the statistical corrections required, selection of individuals with extreme phenotypes and belonging to a population isolate, use of pedigrees, proof of functionality and animal models.

A functional stop codon (C20T-Q20*) in the *HTR2B* gene was identified via deep sequencing of Finnish male violent offenders and controls [77]. The *HTR2B* stop codon led to RNA variable nonsense-mediated decay and blocked expression of the receptor protein. The case group comprised individuals who underwent psychiatric evaluation for the extreme nature of their crimes (homicides, batteries, assaults, arsons) when they were initially incarcerated. Controls were free of psychiatric disorders.

We analysed a Finnish cohort because of its founder population characteristics. Peltonen *et al.* [135] described how in the Finnish population the genetic heterogeneity of medical genetic diseases is dramatically reduced. Frequency of certain rare diseases (Finnish disease heritage) and disease alleles is dramatically increased and other alleles are absent or rare. Directly relevant to the search for causal rare alleles, a single major mutation accounted for more than 70 per cent of disease chromosomes, and in some medical genetic diseases represented up to 98 per cent of disease alleles.

The violent offenders belonged to a cohort with extreme behavioural characteristics that lead to the completion of violent acts. This was the same cohort studied by Linnoila *et al.* [88], who reported that CSF 5-HIAA was reduced only in individuals whose aggressive behaviour and violence was impulsive. The individuals sequenced were diagnosed with ASPD, BPD and IED and were selected among the cases with the highest BGHA scores. They also had significantly higher impulsivity scores on the Karolinska Scales of Personality. The *HTR2B* stop codon was enriched in individuals with a history of impulsive, non-premeditated, violence. The presence of the stop codon seems to play a role in

releasing impulsive aggression under conditions where it is known that impulse control is impaired, especially alcohol intoxication. In an epidemiologic sample, it was observed that Finnish male carriers of the stop codon performed less well on the Digits forward and backward task, a neuropsychological test assessing working memory and accessing executive cognitive function. The stop codon also cosegregated with ASPD in eight informative families. Although the *HTR2B* stop codon is associated and co-segregates with disorders characterized by impulsivity, the presence of the genetic variant is necessary but not sufficient to explain severe episodes of impulsive behaviour: male sex, testosterone levels, the decision to drink alcohol and probably other factors, such as stress exposure, have important roles.

A knockout mouse model offered the opportunity to test the predictive validity of the effect of the *HTR2B* stop codon on impulsivity observed in people. *Htr2b*^{-/-} mice displayed increased delayed discounting, high novelty seeking and high reactivity to novelty. The broad effect of the *Htr2b*^{-/-} may be due to the pleiotropic actions of the 5-HT_{2B} receptor but also validates the effect of the stop codon on impulsivity observed in humans. Interestingly in *Htr2b*^{-/-} male mice, a significant increase in plasma testosterone levels was observed. In humans as well, although in a limited number of individuals, an increase in CSF testosterone levels was also observed in stop codon carriers. This raises the possibility of an interaction between the *HTR2B* stop codon and testosterone contributing to impulsive behaviours, as reported between MAOA and testosterone in this same Finnish population [65], although in this instance, the gene × endocrine interaction may be reverse causal.

Illustrating the power of genomic approaches to define novel pathways, in this study sequencing led to the identification of a novel genetic variant in a gene whose role in complex behaviour was scarcely explored. The *HTR2B* gene, on chromosome 2 (2q36.3–q37.1), encodes the serotonin 2B receptor, a G protein-coupled receptor. Serotonin 2B receptors are located in the stomach fundus, uterus, vascular endothelial and vascular and enteric smooth muscle [136] and are widely expressed in the human brain [77,137–139]. The function of the 5-HT_{2B} receptor in the brain is mainly unknown and few studies had attributed a direct effect of the 5-HT_{2B} receptor in the CNS. A preferential 5-HT_{2B} agonist was shown to increase food consumption, and reduce grooming, and microinjection in the medial amygdala elicited anxiolysis in the social interaction model [140]. The 5-HT_{2B} receptor had been proposed to have a role in the regulation of food intake, and recently it was reported that 5-HT regulates appetite, possibly via 5-HT_{2B} receptors on hypothalamic neurons [141]. *HTR2B* mRNA and protein are expressed in serotonin transporter-expressing neurons of the mouse raphe nuclei [142]. Launay and colleagues described how 5-HT_{2B} pre-synaptic receptors modulate serotonin reuptake by promoting the phosphorylation of the serotonin transporter in these neurons. Furthermore, serotonergic neurons of the dorsal raphe nucleus project to the ventral tegmental area and to the nucleus accumbens and impact dopaminergic neurotransmission [143]. The regulation of mesolimbic dopaminergic activity by 5-HT and its receptors plays an important role in the reinforcing effects of drugs of abuse [144]. Doly *et al.* [139,145] have shown that 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy)-induced 5-HT release was dependent on pre-synaptic 5-HT_{2B} receptors in raphe neurons. 5-HT_{2B} antagonists or genetic

ablation of the gene blocked the effects of MDMA on serotonin release and behaviour. Auclair *et al.* [146] described the impact of 5-HT_{2B} antagonists (such as LY 266097) on dopamine outflow from the ventral striatum but not on nigrostriatal outflow. Antagonists also significantly diminished dopamine (DA) outflow in the nucleus accumbens induced by haloperidol and amphetamine, two drugs known to activate DA neuronal function through different cellular mechanisms. The selective ability of 5-HT_{2B} receptor antagonists to reduce mesoaccumbal DA outflow without altering the function of the nigrostriatal DA system is of great interest, and could have important therapeutic implications.

The *HTR2B* stop codon is less limited in its distribution compared with the *MAOA* stop codon found by Brunner *et al.* in one Dutch family, but has not been reported outside individuals of Finnish ancestry [77]. The identification of a genetic variant associated with impulsivity in a founder population revealed a role for the *HTR2B* gene in behaviour and suggests the value of further studies of this gene and its other genetic variations in other populations and in behaviours associated with impulsivity.

12. Conclusions

As described, impulsivity is a heritable, disease-associated trait, useful as an endophenotype for gene discovery. Impulsivity is, however, not a unitary construct and, as discussed, multiple laboratory behavioural tasks and self-reported measures are used to assess different aspects of impulsivity. On the other hand, it is also true that there is no one gene that will be identified as an 'impulsivity gene', since the action of most genes is pleiotropic. In the quest to identify common and rare genetic variants influencing behaviour, deep phenotyping, extreme phenotypes, exposed populations and affected families all appear to be invaluable. Multilevel approaches that may include whole genome strategies, candidate gene studies and proof of molecular functionality of the genetic variation and evaluation of effects in animal models provide routes to validation. As illustrated by the *HTR2B* and *MAOA* stop codons, use of isolated populations with founder characteristics and individual families is highly beneficial to reduce genetic heterogeneity, and to enable the collection of enough individuals with a rare variant to evaluate the effect of the allele on a complex phenotype.

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