Methods

Search strategy

We searched PubMed and Medline databases in September 2018 to identify previous articles related to adult/ adolescence reward processing and addiction. We excluded any grey literature.

Our initial search used the following terms: ((adult OR adolescence)) AND (reward, addiction, (hedonic OR incentive OR impulsive), (substance OR drug)).

Selection of literature

We discarded duplicates and non-English papers due to lack of resources to translate. Any articles that were clearly irrelevant were discarded immediately. We also discarded reviews, opinion pieces, conference/ poster abstracts, case reports and commentaries which did not contain original research.

All authors then read the title and abstract of each remaining article to check for relevance to our review. We also searched the references of relevant papers and identified further publications which were not captured within our original search but were still relevant to our discussion. FK then reviewed all identified articles to ensure they were relevant to our review.

Articles that were deemed relevant were those which contained quantitative or qualitative research on addition or reward in animal models or human volunteers. We excluded papers in which the outcomes discussed were not related to addiction or reward. We did not exclude articles if there was no mention to substance or drug misuse – articles focused on other forms of addiction (e.g. gambling) or reward mechanisms (e.g. sex) still contain relevant findings on this behavior's neurocircuitry.

Data extraction

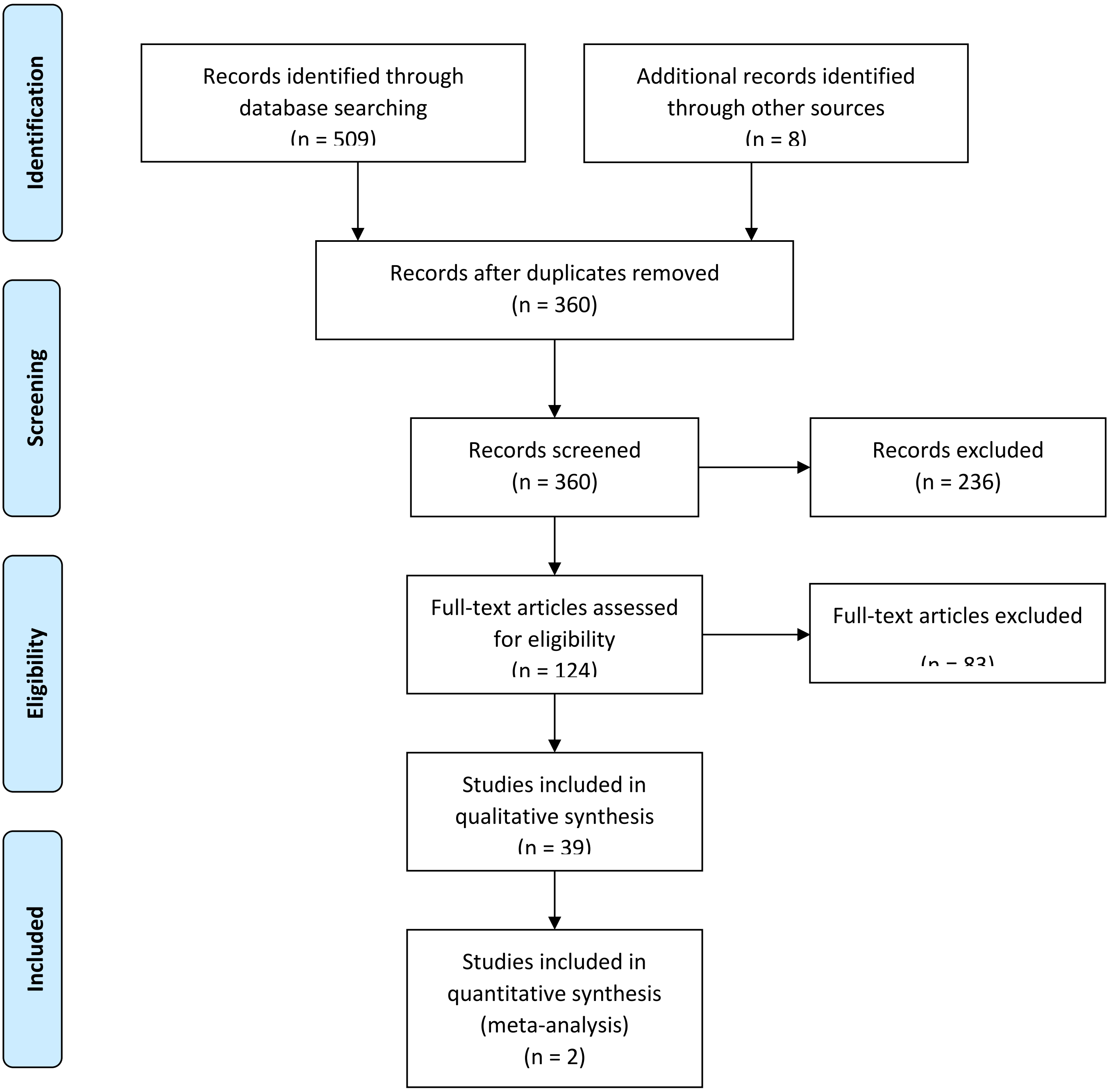
For each article, we extracted the reference, type of study, whether animal or human models, sample size and the relevant findings.

Results

Supplementary Figure 1 shows the search and exclusion process according to PRISMA guidelines.

The search initially yielded 509 articles, 141 of which were duplicates or non-English. A further 8 were added after searching article references. Examination of abstracts and titles led to the exclusion of 236 articles, leaving 124 full texts to be examined for relevance. Of these, 41 articles (including 2 meta-analyses) met inclusion criteria, with 28 studies on animal models and 16 on humans. This is summarized in Supplementary Table 1.

Supplementary Figure 1



Supplementary table 1

Study	Design	Model	Participants	Relevant findings
Harden (2011)[5]	Longitudinal cohort study	Human	7,640 aged between 12 – 24 years	Impulsivity and sensation seeking showed substantial individual person-to-person differences. The correlation between age-related changes in these behaviors was not significant
Urošević (2012)[6]	Longitudinal cohort study	Human	184 aged between 9 to 24 years	Increased reward sensitivity from early to late adolescence and decline in early twenties (associated with decrease nucleus accumbens volume)
Ersche (2013)[9]	Randomized control trial	Human	50 biological sibling pairs	Increased sensation-seeking traits associated with abnormal orbitofrontal and parahippocampal volume in individuals dependent on stimulant drugs/ used cocaine
Belin (2008)[10]	Randomized control trial	Animal	40 adult rats	Evidence that a shift from impulsivity to compulsivity occurs during the development of addictive behavior
Berridge (1998)[21]	Randomized control trial	Animal	38 rats	Affective reaction patterns remain normal even after complete depletion of dopamine from striatal/ accumbens dopamine systems
	Randomized control trial	Animal	8 rats	Severe dopamine depletion did not disrupt the acquisition/ expression of a shift from hedonic reactions to aversion
	Randomized control trial	Animal	6 rats	Diazepam did not alter aversive or hedonic reactions
Wassum (2011)[22]	Randomized control trial	Animal	29 rats	Infusion of mu opioid receptor antagonist into basolateral amygdala (BLA) blocked the normal increase in sucrose-seeking response. Similar treatment with other antagonists were without effect. Thus, shifts in endogenous opioid transmission in the BLA mediate changes in incentive value and compulsive behavior
	Randomized control trial	Animal	35 rats	
	Randomized control trial	Animal	32 rats	
	Randomized control trial	Animal	23 rats	
Hernandez (2007)[24]	Randomized control trial	Animal	6 male rats	Tonic DA signaling is insensitive to the predictability of rewards
Di Chiara (1988)[25]	Randomized control trial	Animal	Unspecified	Drugs that are rewarding in animals and humans preferentially increase synaptic dopamine concentrations in the mesolimbic system
Pfaus (1999)[26]	Randomized control trial	Animal	6 male, 6 female rats	Dopamine increased in the accumbens when males were placed in a novel mating chamber and increased in the striatum during copulation
Hoebel (1983)[27]	Randomized control trial	Animal	20 rats	Amphetamine in the nucleus accumbens activates a local mechanism for response reinforcement
Yokel & Wise (1976)[28]	Randomized control trial	Animal	53 male rats	Dopamine receptor blockade interfered with the reinforcing effects of amphetamine

Ettenberg (1982)[29]	Randomized control trial	Animal	25 male rats	Pretreatment with either naltrexone or flupenthixol increased heroine and cocaine self-administration, suggesting independent neural substrates are responsible for the reinforcing actions of both drugs
Pecina (1997)[31]	Randomized control trial	Animal	8 male rats	Pimozide produces a sensorimotor impairment of taste reactivity patterns but does not shift taste palatability toward anhedonia or aversion.
Doyle (1993)[32]	Randomized control trial	Animal	12 rats	Morphine enhances feeding by increasing the hedonic palatability of food (no change to aversion)
Liggins (2012)[33]	Randomized control trial	Human	49 aged 21.9±3.7 years	The results suggest that dopamine neurotransmission does not directly influence positive mood in humans
Difeliceantonio (2012)[33]	Randomized control trial	Animal	81 female rats	Opioid/ dopamine injection into neostriatum amplified incentive towards previously learned Pavlovian cue
Wassum (2009)[38]	Randomized control trial	Animal	Rats (unspecified)	Changes in palatability and in the incentive value assigned to rewarding events seem to be mediated by distinct neural processes.
Castro (2014)[39]	Randomized control trial	Animal	84 male rats	A rostrodorsal hotspot in the nucleus accumbens generates opioid-induced hedonic behavior and a separate coldspot mediates hedonic suppression
Ziauddeen (2013)[41]	Multi center group study	Human	63 aged between 18-60 years	Treatment with a mu-opioid receptor antagonist caused reduction in hedonic responses to dairy products and reduced caloric intake
Giuliano (2013)[43]	Randomized control trial	Animal	74 adult rats	μ-opioid receptor antagonist treatment caused a decrease in cocaine seeking and may be a target for addiction treatment
Brauer (1996)[46]	Randomized control trial	Human	15 between 21 and 35 years	A dopamine antagonist did not affect responses to amphetamine, suggesting they do not interact at the receptor level
Colasanti (2012)[47]	Randomized control trial	Human	12 aged 36.5±11.9 years	Amphetamine administration induces endogenous opioid release in different areas of human brain e.g basal ganglia, frontal cortex areas, and thalamus
Giuliano (2012)[48]	Randomized control trial	Animal	12 Rats	Addition of a μ-opioid receptor antagonist reduced the impact of high hedonic value on binge eating
Cambridge (2013)[50]	Randomized control trial	Human	63 aged 18 to 60 years	Addition of a μ-opioid receptor antagonist significantly reduced pallidum/putamen responses to pictures of high-calorie food and a reduction in motivation to view images of high-calorie food
Burton (2013)[51]	Randomized control trial	Animal	10 juvenile and adult rats	Amphetamine injections reduced response to a conditioned stimulus (no difference with age)
				Injections of D1 and D2 dopamine receptor antagonists diminished incentive motivation in adolescent rats more than in juveniles
Silverman (2016)[52]	Meta-analysis	Human	830 participants in 26 studies	fMRI results reveal regions involved in adolescent reward processing are similar to that found in adults – ventral and dorsal striatum, insula, and posterior cingulate cortex. Unlike adolescents,

				adults also activate executive control regions of the frontal and parietal lobes during motivated activity
Alarcón (2017)[54]	Longitudinal study	Human	167	Increased motivation and salience of reinforcers is linked with more robust striatal blood oxygen level-dependent response, independent of sex hormone levels.
Cohen (2010)[55]	Randomized control trial	Human	67 aged between 8 and 30 years	Found increased reward-related neural activity during adolescence by demonstrating that this finding is specific to prediction error, reflecting phasic dopamine signaling
Bjork (2010)[56]	Randomized control trial	Human	48, 24 aged 12 – 17, 24 aged 22 – 42	Maturational differences in incentive-motivational neurocircuitry: 1) may be sensitive to nuances of incentive tasks or stimuli, such as behavioral or learning contingencies, and 2) may be specific to the component of the instrumental behavior
Geier (2010)[57]	Randomized control trial	Human	34, 18 aged 13 – 17, 16 aged 18 – 30	Found limitations during adolescence in reward assessment and heightened reactivity in anticipation of reward compared with adults. heightened activity in the frontal cortex along the precentral sulcus was also observed in adolescents during reward-trial response preparation, suggesting reward modulation of oculomotor control regions supporting correct inhibitory responding.
Luijten (2017)[58]	Meta-analysis	Human	643 individuals across 25 studies	During reward anticipation, individuals with substance and gambling addictions showed decreased striatal activation compared with healthy control individuals. During reward outcome, individuals with substance addiction showed increased activation in the ventral striatum, whereas individuals with gambling addiction showed decreased activation in the dorsal striatum compared with healthy control individuals.
Besson (2013)[66]	Randomized control trial	Animal	144 juvenile rats	High impulsivity (cocaine) rats exhibited decreased dopamine mRNA in the mesolimbic pathway and 5-HT mRNA in striatal and prefrontal areas
Besson (2009)[67]	Randomized control trial	Animal	96 rats	Dopamine D2/3 receptor antagonist increased the level of impulsivity when infused into the nucleus accumbens core but decreased impulsivity when injected into accumbens shell
Olmstead (2009)[68]	Randomized control trial	Animal	96 μ and δ opioidR KO mice	Results suggest that mu-opioid receptors enhance, whereas delta-opioid receptors inhibit, motor impulsivity
Boileau (2006)[71]	Longitudinal study	Human	10 aged 25.8±1.8 years	Sensitization to amphetamine can be achieved in healthy men in the laboratory. This phenomenon is associated with increased dopamine release and persists for at least one year.
Di Ciano (2003)[72]	Randomized control trial	Animal	39 naive rats	Administration of a D3 dopamine receptor antagonist decreased impulse for cocaine,

				suggesting a selective role of these receptors in motivational aspect of conditioned stimuli
Belin (2011)[73]	Randomized control trial	Animal	40 adult rats	Addiction is sustained by two vulnerable phenotypes: a ‘drug use prone' phenotype which brings an individual to develop drug use and an ‘addiction prone' phenotype, which facilitates the shift from sustained to compulsive drug intake and addiction
Corbit (2012)[74]	Randomized control trial	Animal	19 rats	Extended alcohol self-administration produces habit-like responding and that response control shifts from the dorsomedial to the dorsolateral striatum
Zapata (2010)[75]	Randomized control trial	Animal	Rats	With more prolonged drug experience, animals transitioned to habitual cocaine seeking. When the dorsolateral striatum (involved in habit learning) was inactivated, drug-seeking reverted to a goal-directed system
Molander (2011)[78]	Randomized control trial	Animal	48 rats	Behavioral impulsivity in rats on a test, which predicts vulnerability for cocaine addiction, is distinct from anxiety, novelty reactivity and novelty-induced stress responses, and thus has relevance for the etiology of drug addiction
Conrod (2010)[80]	Randomized control trial	Human	5302 aged between 13 to 16 years	Brief, personality-targeted interventions can prevent the onset and escalation of substance misuse in high-risk adolescents