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A Systematic Review of the Valproic-Acid-Induced Rodent Model of Autism

Devahuti Chaliha[a] Matthew Albrecht[a] Mauro Vaccarezza[b] Ryu Takechi[a]
Virginie Lam[a] Hani Al-Salami[b] John Mamo[a]

[a]School of Public Health, Curtin Health Innovation Research Institute, Perth, WA, Australia; [b]School of Pharmacy and Biomedical Science, Curtin Health Innovation Research Institute, Perth, WA, Australia

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Abstract
Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by repetitive behaviours, cognitive rigidity/inflexibility, and social-affective impairment. Unfortunately, few pharmacological treatments exist to alleviate these socio-behavioural impairments. Prenatal administration of valproic acid (VPA) has become an accepted animal model of ASD and has been extensively used to explore new pharmacotherapies in rodents. We conducted a systematic review of the behavioural impairments induced by the VPA model in rodents, with specific reference to 3 core socio-behavioural alterations associated with ASD: repetitive behaviours, cognitive rigidity/inflexibility, and social-affective impairment. We systematically reviewed studies attempting to alleviate these core behavioural alterations using pharmacological means. We include 132 studies exploring the prenatal effects of VPA in rodents. Gestational exposure to VPA in rodents has significant effects on rodent-equivalent measures of the 3 core behavioural traits characteristic of ASD in humans, inducing social impairments, repetitive behaviour, and cognitive rigidity/inflexibility after birth. This model's validity has seen it used to test potential drug treatments for ASD and is likely to continue doing so. We conclude the rodent VPA model may be suitable to examine future therapeutic interventions for ASD, providing an overview of the progress made so far.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder manifesting early in development and characterised by impairment of social interaction and communication, and restricted and repetitive/stereotyped patterns of behaviour [1]. For more specific analysis, we have extracted and explored a triad of behavioural symptoms, including social reciprocal communication and interaction impairment, restrictive or repetitive behaviour (such as motor stereotypies) or interests, and cognitive rigidity or inflexibility [1, 2], as the separate behaviours comprising these 2 broad sets considered core to ASD. There are currently no pharmacological treatments approved by the Food and Drug Administration (FDA) for these core impairments of ASD [3]. Rather, 2 currently approved medications to treat ASD, antipsychotics aripiprazole and risperidone, principally target the accessory traits of irritability and aggressiveness [4].

karger@karger.com
www.karger.com/dne

John Mamo
School of Public Health
Curtin Health Innovation Research Institute
Kent Street, Perth, WA 6102 (Australia)
J.Mamo@curtin.edu.au

A significant number of off-label medications have also been utilised, such as alpha-2 agonists, mood stabilisers, norepinephrine-reuptake inhibitors, serotonin-reuptake inhibitors, other antipsychotics, and opioid-receptor antagonists [5, 6]. However, these have insufficient evidence of efficacy from randomised clinical trials, or only target accessory symptoms of ASD, such as irritability and hyperactivity [5, 6]. Developing appropriate pharmacological treatments is further complicated by the high prevalence of comorbid conditions in ASD, including affective disorders (such as anxiety, or depression) or neurological disorders (such as epilepsy), often requiring additional prescriptions [7, 8]. A number of complementary and alternative medicines, including Korean red ginseng [9, 10] and purple rice with silkworm pupae [11], have been shown in small pilot trials to improve symptoms of ASD, including stereotypies, social behaviour, and anxiety (Table 1). However, they do not yet have the evidence base required for more widespread adoption [12].

There exists a need to develop effective pharmacological treatments for ASD, capable of targeting its core behavioural impairments. Animal models provide a means to examine the potential impact of pharmacological treatments, prior to human testing. However, this relies on the animal model possessing construct, face, and predictive validity to extrapolate to humans [13]. In order for animal models of ASD to therefore be effective, they must (1) hold an empirical and theoretical relationship to ASD, having behaviours that are unambiguous and homologous between species (construct validity), (2) resemble ASD in its clinical features (face validity), and (3) correctly predict clinical treatments for ASD (predictive validity) [14]. The administration of valproic acid (VPA) (2-propylpentanoic acid) to pregnant rodent mothers at a critical time during gestation is a widely used animal model of ASD [15], derived from pharmaco-epidemiological findings in humans showing a strong association between maternal gestational VPA use (e.g., for epilepsy, mania, and migraine) and the later development of ASD in the child [16–18].

The epidemiological findings suggest a critical period during embryogenesis that contributes to the altered development leading to ASD [19]. Similar timing effects of VPA exposure are also observed in rodents [20, 21], with effective treatments likely being associated with processes related to neural tube closure [22]. Hypoplasia of the pons in the brainstem, occurring immediately following neural tube closure, has been proposed as one of the unifying causes of autism phenotype [23].

The VPA rodent model appears to possess face validity and construct validity to model human ASD, as VPA-exposed rodents seem to express a similar superficial behavioural phenotype as people with ASD [24]. Given that gestational administration of VPA to rodents may provide an ideal means to evaluate novel treatments for ASD, there is a clear need to understand and characterise the behavioural effect of gestational VPA exposure. This topic has been reviewed previously [15, 25–27], indicating that VPA has good construct, face and predictive validity to simulate a rodent model of ASD. However, none of these reviews catalogued systematically all the VPA studies that have been done to date or assessed a list of comparable therapies against each other for the same parameters. Consequently, there is an uncertainty as to the quantitative effects of gestational VPA on the postnatal behaviours comprising ASD, as well as the quantitative effects of different drugs to alleviate ASD trialled so far in the literature. A new systematic review was necessary for prospective therapeutic-drug investigators to measure up their chosen ASD therapeutic to others' progress made so far. With our present study, we aimed to highlight rodent studies that investigated animal analogues of 3 core socio-behavioural differences present in people with ASD in the prenatal VPA model. We further systematically reviewed the literature by applying novel pharmacological treatments to the VPA model.

Methods

Study Design

A systematic review of the literature exploring how VPA influences the presentation of ASD-like behavioural changes in rodents, and the pharmacological treatment of these changes, was conducted.

Search Strategy (Table 2)

Six electronic databases including ProQuest, PsychInfo, Scopus, Medline, Web of Science, and PubMed (between the earliest recorded date and May 19, 2020) were analysed. The search strategy included a combination of keywords and MESH terms which were combined using "OR" or "AND." Terms included autis*, ASD, pervasive development* disorder*, rat, mouse, rodent, mice, behav*, charact*, respons*, valproic acid. Search strategies were tailored to each database.

Study Inclusion and Exclusion Criteria

This systematic review identifies literature examining the effects of prenatal VPA administrations in rodents with core equivalent behaviours affected in ASD as outlined by the DSM-5 and ICD-10: social impairment, repetitive behaviour, and cognitive rigidity [1, 2]. To this end, the following behavioural tests were included: for social impairments, (1) ultrasonic vocalisation; (2) social prefer-

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Table 1. ASD behaviours in rodents administered with valproic-acid, compared with control rodents, in their respective studies

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Ahn [97], 2014	5	Rat	Males	15	500	i.p.	12.5	35–38		24 h	Direct attacks to nape, responses to these (complete/ partial/horizontal rotations and evasions)						5: Lower play-fighting attack frequency, more complete-rotation defensive responses	5: Fewer evasions of nape attacks
Al-Amin [98], 2015	2, 3, 6	Mouse	Both	20	600	i.p.	12.5	20–26				Exploration					2: Less time with, fewer explorations of, conspecific. 3: Decreased sniffing frequency and time with unfamiliar. 6: Increased mean speed, global activity, total distance travelled. Decreased periphery time, increased centre time and centre hypolocomotion	2, 3, 6: NA
Ali [43], 2013	2	Rat	Males	8	800	p.o.	12.5	21									2: Less time with conspecific, more time in object chamber	2: NA
Al Sagheer [36], 2018	2, 6	Mouse	Both	116	450	i.p.	12.5	30–45				Number of rearings, time spent self-grooming					2: Males: similar durations in both chambers (controls: more time in social chamber). Females: no effect. 6: More time self-grooming. Males made fewer rearings	2: Females: not affected. 6: VPA females did not have fewer rearings
Anshu [99], 2017	2, 3	Rat	Both	58	450	i.p.	12.5	90–120									2: Both sexes: more time with object than conspecific. 3: No effect	2, 3: NA
Bambini-Junior [100], 2011	2, 3, 8	Rat	Both	16–36	600	i.p.	12.5	35–50, 80–115					Y	Food reward	Half Froot-Loop	No mention	2: PD 35, 50: less time exploring conspecific, more time with conspecific than object. 3: Less interest to approach unfamiliar. 8: Longer time to learn to switch arms in reversal phase	2: No difference in times spent in each chamber, or exploring object. 3: Still more time with unfamiliar than familiar. 8: No learning difference in acquisition phase (as expected in all rats). When arm order reversed and test repeated, no difference seen (as expected in all rats)
Bambini-Junior [101], 2014	2, 3	Rat	Males	19–26	600	i.p.	12.5	35–50									2: PD 35, 50: similar time in both object and conspecific chambers. 3: No difference between times spent in familiar and unfamiliar chambers, or explorations of familiar and unfamiliar conspecifics	2: Insignificant trend to spending more time with object than conspecific. 3: Also least time spent in central chamber
Banerjee [102], 2014	4, 5, 6	Rat	Males	28–66	500, 600	i.p.	12.5	65–90		24 h	Time spent in social zone, sniffing conspecific, latency to first entry to social zone, longest time in social zone	Total entries to centre, time spent in centre, distance travelled in centre, mean distance travelled					4: 500 mg/kg: at sampling, more time exploring left than right objects. 6: 600 mg/kg: decreased centre entries and centre distance travelled. 500 mg/kg: decreased centre entries, time, distance travelled. 5: Less time in social-interaction zone, more time/latency to first enter social zone	4: 500, 600 mg/kg: no effect (more time spent with novel object, similar time as control). 6: 600 mg/kg: insignificant trend of decreased centre time; no difference in mean distance travelled. 500 mg/kg: no difference in mean distance travelled. 5: Mean distance travelled in social zone did not differ

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Baronio [103], 2015	2, 3, 7	Mouse	Both	16	500	i.p.	11	50									2: Similar times exploring both object and conspecific. 3: Similar times exploring familiar and unfamiliar. 7: More marbles buried	2: Like controls, less time spent in central chamber. 3: Also least time spent in central chamber. 7: NA
Barrett [31], 2017	1, 2, 3, 6	Rat	Both	20–52	500, once daily	p.o.	11–13	7, 11, 35	0–2			Durations in, entries into, each zone					1: Females, PD 7: shorter call lengths. PD 11: fewer pup calls. PD 7, 11: higher call frequency. 2: Females: less exploration time in centre. Both sexes: fewer entries into conspecific quadrant. 3: Males: fewer approaches to and less time near unfamiliar, more time in empty arena, less time in and fewer enterings into unfamiliar area. 6: Females: decreased centre-exploration time	1: PD 7: all durations not shorter between males. PD 11: Call durations not shorter between sexes. PD 7: not fewer calls. 2: No effect on times in social zone. 3: females: no effect. 6: Not reported in males
Bertelsen [44], 2017	5	Rat	Males	78	20, 100, once daily	i.p.	12+	29–34		3.5 h	Numbers of pinnings and pouncings						5: 20 mg/kg daily: less pinning	5: 100 mg/kg: no difference in pinning. No differences in pouncing (either dose)
Bringas [104], 2013	6	Rat	Males	18	500	i.p.	12.5	21, 35, 70				Locomotor activity by beam breakage; infrared beam sensor for number and durations of head dippings into holes					6: PD 21: hyperlocomotion. PD 70: locomotion stabilised in 60 min. (instead of declining as in controls), hyperlocomotion; longer head-dipping durations, fewer head-dippings, more time to first head dip (exploratory behaviour). PD 21, 70: overall increase in locomotor activity	6: Both groups initially had increased locomotor activity. PD 21, 35: locomotor activity soon declined in 30 mins. in both groups; head-dipping durations not longer, not number of head dippings lower, latency to first head dip not longer, than controls
Campolongo [105], 2018	2, 4, 5, 8	Mouse	Males	26–44	600	s.c.	12.5	21, 60, 84, 119		40 min	Crawling, approaching (play), sniffing/following, sitting adjacently, social grooming; time exploring, self-grooming, sitting alone		Y		Spontaneous alternation	NA	2: Less interaction time with conspecific. 4: No effect. 5: Less frequent play solicitation, less anogenital sniffing. 8: Less alternation, exploration (distance travelled)	2, 8: NA. 4: No differences in times spent with novel object. 5: No difference in time spent sitting adjacently/alone, social/self- grooming, exploring
Cartocci [106], 2018	1, 2	Rat	Males	12–24	500	i.p.	12.5	9, 35, 90	1								1: Fewer calls. 2: PD 35, 90: decreased time sniffing conspecific	1, 2: NA.
Castro [107], 2017	2, 3, 7	Mouse	Males	16	600	i.p.	11	70									2: More time in object than conspecific chamber. 3: Similar times exploring familiar and unfamiliar. 7: More marbles buried	2, 3, 7: NA

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Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Cezar [108], 2018	1, 5, 8	Rat	Males	20	400	i.p.	12.5	11, 29, 30	1	9 days	Frequency of pinning, darting, crawling, rearing; duration of following, sniffing		T		Spontaneous alternation	NA	1: Decreased total and maximal call durations, fewer calls, increased mean silence duration. 5: Lower pinning frequency, fewer darting movements. 8: Decreased spontaneous alteration, increased repetitive choosing of same arm	1, 5, 8: NA
Chau [109], 2017	2, 3	Mouse	Males	12	600	i.p.	12	28, 35, 42, 49									2: More time in empty chamber, less time with conspecific. 3: More time with familiar than unfamiliar	2, 3: NA
Cheaha [32], 2015	1	Mouse	Males	20	600	s.c.	13	12	2–3								1: Fewer calls, lower frequency and density of calls	1: NA
Cheaha [110], 2015	1, 6	Mouse	Males	16–24	600	s.c.	13	12, 30	2–3			Spontaneous self-grooming					1: Decreased call rate. 6: Increased self-grooming time	1, 6: NA
Cho [63], 2017	2, 3	Rat	Both	77	400	s.c.	12.5	28–42									2: Less time interacting with conspecific. 3: Males: less time with unfamiliar, but still more time with unfamiliar than familiar	2: No effect on time spent with conspecific or object. 3: NA
Choi [76], 2016	2, 3, 6, 7	Mouse	Males	19–116	300	NA	10	28, 70, 91				Total distance moved, movement duration					2: 1st generation: less time in conspecific chamber, more time in empty chamber. F2 and F3 generations: more time in empty chamber. 3: F1, F2, F3: more time in familiar chamber, less time in unfamiliar chamber. 6: F1, F2, F3: more distance moved, more activity in centre. 7: 1st and 3rd generations: more marbles buried	2, 3, 6: NA. 7: No significant effects in 2nd generation
Choi [111], 2014	6	Rat	Males	18	400	s.c.	12	28				Total distance moved, number of rearings					6: Hyperlocomotion, increased rearing frequency, distance moved in centre	6: NA
Chomiak [112], 2014	4	Rat	Males	11	500	i.p.	13.5	69–90									4: No effect	4: No difference in total exploration time
Codagnone [113], 2015	5, 6	Rat	Males	12–20	500	i.p.	11.5	30–35		3.5 h	Latency and number of pinnings, sniffing, following/ approaching, mounting/ crawling over	Number of rearings and holepokes, self-grooming episodes					5: PD 35: fewer holepokes, more repetitive self-grooming, fewer pinnings and sniffings 6: Fewer holepokes. Increased stereotyped self-grooming	5: No differences in total following/approaching, crawling/mounting behaviours; also similar latencies to pinning and sniffing. 6: No difference in rearings

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Cohen [114], 2013	5	Rat	Both	109	350	i.p.	13	28, 42, 75		30 min	Frequencies of sniffing, crawling under/over, social grooming, following, chasing, nape play attacks, pinning, crossovers from/ away from conspecific						5: More play fighting and social investigation	5: No difference in contact behaviours or social preference (crossovers to/ away from conspecific). No difference in number of crossovers
Cuevas-Olguin [115], 2017	5, 8	Rat	Both	68	600	i.p.	12.5	61–65		3.5 h	Time non-anogenital sniffing/licking, crawling/climbing, following/ approaching, anogenital sniffing		Y		Spontaneous alternation	NA	5: Fewer sniffings, crawlings/mountings, anogenital sniffings. 8: Decreased arm alteration	5: Similar counts of following. 8: NA
Dai [116], 2018	1, 2, 3, 6	Rat	Males	25–38	600	i.p.	12.5	7, 35–40	NA			Total self-grooming time					1: Fewer calls. 2: Spent similar times on both sides (controls: more on social). Decreased sniffing time. 3: No effect. 6: Longer self-grooming time	1, 2: Insignificant trend towards shorter calls. 3: More time spent with unfamiliar than familiar. 6: NA
Dai [117], 2017	2, 6	Rat	Males	12	400	i.p.	12.5	33–35				Duration in centre, standing and grooming					2: Less time interacting with conspecific. 6: Increased self-grooming rate and centre time, decreased standing times	2, 6: NA
Degroote [61], 2014	5, 6	Rat	Both	20–38	600	p.o.	12	20–40		Nil	Time playing, pursuing, sniffing, grooming conspecific	All trajectories					5: Males: total mean time and number of interactions decreased. VPA females: no longer spending less time interacting than control males. 6: Increased distance travelled, increased time of locomotion	5: Females: not fewer interactions. 6: No difference between males and females
De Mattos [118], 2020	5,6	Rat	Both	20	800	p.o.	12.5	30–40			Number of times "resident" moved toward "stranger", the interaction time (resident to stranger: sniffed, touched, licked, or climbed into same containment grid)	Total number of squares crossed with all paws					5: Reduced social interaction time. 6: Increased latency in open field	5, 6: NA
de Theije [119], 2014	2	Mouse	Both	41	600	s.c.	11	28									2: Males: decreased social interaction, less time in interaction zone	2: Females: not affected. Locomotor activity: not affected
de Theije [37], 2014	2	Mouse	Males	12	500	s.c.	11	28									2: Decreased social interaction, less time in interaction zone	2: NA
Du [120], 2017	5, 6	Rat	Males	10–20	600	i.p.	12.5	21, 32, 42		3.5 h	Latency to, total time of, and frequency of pinning	Total duration of self-grooming					5: Increased latency to, and duration of, pinning. 6: PD 32, 42: increased self-grooming time	5: No change in pinning frequency. 6: NA

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Dufour-Rainfray [121], 2010	2, 3	Rat	Males	24	600	i.p.	9	31									2: More crossovers with higher locomotion, less social and exploratory behaviour. More time spent with conspecific than object. Fewer social approaches. 3: More time in unfamiliar than central compartment, more crossovers between compartments. More time in central compartment than controls	2: NA. 3: Similar times in familiar and unfamiliar compartments, to controls
Edalatmanesh [122], 2013	5, 8	Rat	Both	76	500	i.p.	12.5	30, 60		"Night before"	Time pinning, following, touching, allogrooming, non-anogenital and anogenital sniffing, hiding (in tube)		Y		Spontaneous alternation	NA	5: Less play behaviour, sniffing/touching (social exploration), more hiding time, less pinning, less sniffing time. Males more affected in sniffing, females more affected in anogenital sniffing. 8: PD 60, 30: constituted more VPA rats entering same arm	5: No differences in following, grooming, number of anogenital inspections. No sex effects in pinning, following, grooming, touching, hiding. 8: NA
Eissa [123], 2018	2, 3, 7	Mouse	Males	12–14	500	i.p.	12.5	21, 51–64									2: Similar times with object and conspecific. 3: Similar times spent with familiar and unfamiliar. 7: More marbles buried	2, 3, 7: NA.
Eissa [124], 2019	6	Mouse	Males		500	i.p.	12.5	51–56				Time spent in the centre and periphery					6: Decreased time in centre	6: No difference in time spent in periphery
Favre [125], 2015	2, 8	Rat	Males	36–107	500	i.p.	11.5	81–123					Y		Spontaneous alternation	NA	2: Less total sniffing time, less time sniffing conspecific. 8: VPA group constituted most rats with consecutive same-arm entries	2: Enriched environments: no effect. 8: In smaller samples, insignificant trend for large effects
Felix-Ortiz [33], 2012	1, 4, 5	Rat	Males	18–41	600	i.p.	12.5	5, 11, 35–40	Multiple	24 h	Time of play fighting, duration of approaching/grooming/sniffing, pinning frequency, number of submissions, pulling, nape-biting, locomotion, self-grooming						1: PD 5: more complex and downward calls. 4: Less time exploring novel object, some increased time exploring familiar. 5: Less approaching, sniffing, grooming of juvenile intruder, more locomotor activity, fewer play attacks to nape	1: PD 11: no effect. 4: Similar durations of total object exploration. 5: No differences in play behaviour or self-grooming
Foley [126], 2012	2	Rat	Males	8	600	i.p.	12.5	91–92									2: PD 72: more time in non-social chambers	2: NA
Foley [127], 2014	2	Rat	Males	5–6	600	i.p.	12.5	91–92									2: Less interaction with conspecific, 30% less time in conspecific chamber	2: NA
Gandal [128], 2010	1	Mouse	Both	52	600	s.c.	13	2, 5, 8, 12	Multiple								1: Fewer calls	1: NA

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Gao [129], 2016	2	Rat	Males	12	600	i.p.	12.5	35–40									2: PD 35, 50: similar times in both object and conspecific chambers	2: NA
Gobshtis [130], 2017	2, 6	Mouse	Males	26	500	i.p.	12.5	49				Total distance walked, duration in centre					2: Less interaction time with conspecific. 6: No effect	2: NA. 6: No difference in total distance walked, duration in centre
Gonzales [10], 2016	2, 3, 6, 7	Mouse	Males	20	300	s.c.	10	23–32				Distance and duration moved					2: Less time in conspecific chamber, more time in empty chamber, less time exploring conspecific than object. 3: More time in familiar compartment, less time in unfamiliar compartment. 6: Increased distance moved. 7: More marbles buried	2: Time spent in central area: no effect. Trend towards higher sniffing duration of object. 3: Time in central compartment: no effect. Sniffing duration towards unfamiliar: no effect. 6: No difference in duration moved. 7: NA
Guo [131], 2018	2, 6	Mouse	Both	12–20	600	i.p.	12.5	35–42				Duration in centre, total distance travelled					2: Less time in conspecific than object chamber. 6: Decreased centre time	2: NA. 6: No mention of change in total distance travelled, or between sexes
Ha [132], 2017	2, 3, 6	Mouse	Males	16–20	600	s.c.	13	21–112				Duration and frequency of self-grooming, time spent in centre and number of centre entries					2: Less time exploring conspecific than object. 3: Similar times spent with familiar and unfamiliar. 6: Increased stereotypic self-grooming (duration and frequency). Decreased centre time and entries	2, 3, 6: NA
Hajisoltani [133], 2019	2, 3	Rat	Males	16	500	i.p.	12.5	33–60		"Night before"							2: Less time spent in conspecific chamber, more time spent in central chamber. 3: Less time spent in unfamiliar chamber, more time spent in familiar and central chambers	2, 3: NA
Hara [75], 2017	4, 5	Mouse	Males	24–26	500	i.p.	12.5	56–57		60 min	Time of face and anogenital sniffs						4: Decreased difference in time exploring novel and familiar objects. 5: Decreased sniffing time towards conspecific	4: Similar total exploration times. 5: NA
Hara [134], 2016	4, 5	Mouse	Males	53–159	500	i.p.	12.5	56		60 min	Time of face and anogenital sniffing						4: Decreased time exploring novel object. 5: Decreased sniffing times	4: Total exploration time: no effect. 5: NA
Hara [135], 2017	4, 5	Mouse	Males	20–24	500	i.p.	12.5	56		60 min	Time of face and anogenital sniffs						4: Decreased time exploring novel object. 5: Decreased sniffing time towards conspecific	4: Total exploration times: no effect. 5: NA
Hara [136], 2015	6	Mouse	Males	12–28	500	i.p.	12.5	56				Paths taken, total travelling distance					6: Hypolocomotion	6: NA
Hill [48], 2015	2, 5, 7	Mouse	Males	16–72	600	i.p.	8.5	84–140		9 weeks	Time retreating or remaining on tube						2: More time with conspecific than object. 5: More losses in social dominance. 7: Fewer marbles buried	2, 5, 7: NA

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Hirsch [47], 2018	5, 6	Rat	Males	17–26	600	i.p.	12.5	46–64		5 min (test rat)	Time nose-nose and anogenital sniffing, flank exploration, following	Duration of spontaneous grooming behaviour					5: Decreased time and number of nose-nose sniffing, following; decreased prosocial interactions, interaction time. 6: More self-grooming time, in 2nd 5 min	5: No difference in anogenital inspection, number/time of flank exploration. 6: No difference within first 5 mins. (rats not habituated beforehand). Similar latencies to start self-grooming
Hirsch [137], 2020	2, 3, 5, 6	Rat	Males	26–32	600	i.p.	12.5	32–38		Nil	Time and number of nose-nose interaction, anogenital inspection, flank exploration, following	Time and number of stereotyped movements (self-grooming behaviour)					2: Spent more time with object than conspecific. 3: No difference. 5: More time completely self-grooming. 6: Less time in central square. Lower number of rearings	3: Both control and VPA rats spent equal times in familiar and unfamiliar chambers. 5: No difference in time incompletely self-grooming. 2, 6: NA
Hou [138], 2018	2, 3, 6	Rat	Male	28–55	600	i.p.	12.5	35–45				PD 40: number of demarcated squares crossed, frequency of rearings, defaecation and urination frequency. PD 35: time spent self-grooming					2: Less time in conspecific chamber and to interact with conspecific. More interaction time with object and time in central chamber. 3: More time in familiar and centre chambers. Less time interacting with familiar and unfamiliar. Less time in unfamiliar chamber. 6: PD 40: fewer central squares crossed. PD 35: more self-grooming	2, 3: NA. 6: PD 40: no difference in total squares crossed. No differences in numbers of defaecations/ urinations. PD 35: NA
Huang [139], 2019	2, 7	Mouse	Male	18	500	i.p.	12.5	56		Nil							2: No preference for object or conspecific (same time spent in each chamber). 7: More marbles buried.	2,7: NA
Kang [51], 2015	2, 3, 6, 7	Mouse	Both	20–21	600	s.c.	13.5	21–112				Self-grooming, jumping, digging					2: Less time exploring conspecific than object, similar times with object and conspecific, less time in conspecific chamber. 3: No effect. 6: Increased stereotypic self-grooming and jumping. Novel bright environment: increased stereotypic self-grooming; familiar dark environment: no effect. 7: No effect	2: NA. 3: Insignificant trend towards less sniffing time and time with unfamiliar, time spent in unfamiliar chamber. 6: Dark environment: no difference in self-grooming, locomotion, rearing. 7: VPA mice did not show more digging (number of diggings or marbles buried)
Kazlauskas [140], 2019	2	Mouse	Both	23–33	600	s.c.	12.5	56–70	8–10	Nil							2: Only male mice had decreased sociability (similar times with object and conspecific)	2: Female mice were not affected (more time with conspecific than object)
Kataoka [141], 2013	5, 6	Mouse	Both	8–35	500	i.p.	12.5, 14.5	28–56		Nil	Time of face and anogenital sniffs, allogrooming, biting, pushing under, sideways posturing, aggressive grooming	Ambulation					5: GD 12.5, males: decreased sniffing time at 28–56 days old. Females: increased sniffing time. 6: GD 12.5: decreased locomotion, rearings, centre entries	5: GD 14.5: no effect. 6: PD 56: no difference in initial locomotor activity, no male-female difference

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Kawase [142], 2018	5	Mouse	Males	24–28	500	i.p.	12.5	56		60 min (test mouse)	Time of face, back, anogenital sniffing, allogrooming						5: Decreased allogrooming and sniffing time	5: NA
Kerr [143], 2013	2, 6	Rat	Males	28–32	600	i.p.	12.5	33–40				Distance moved, duration in centre zone					2: Males: less time in conspecific chamber, more time in central chamber. 6: Decreased distance moved, decreased duration in centre	2: Locomotor activity: no effect. 6: NA
Kerr [41], 2016	2	Rat	Both	NA	600	i.p.	12.5	42–44									2: Less time in conspecific quadrant, more time in object quadrant. Males: less environmental exploration, more stereotypies. Females: less environmental exploration	2: Females: not more stereotypies
Khalaj [144], 2018	2, 3, 6	Rat	Males	14	500	i.p.	12.5	28–30				Number of crossings across demarcated lines, total distance travelled, duration in centre					2: More time in empty chamber, less time in conspecific chamber. 3: More time with familiar rat, less time with unfamiliar. 6: Decreased durations in centre and periphery, increased locomotor activity	2, 3: NA. 6: Total distance travelled, not mentioned
Khongrum [145], 2015	6	Rat	Both	20	400	s.c.	14	40				Grooming, rearing, durations in periphery and centre					6: Decreased centre time, increased periphery time	6: No changes in rearing and grooming
Kim [146], 2011	2, 3	Rat	Both	24–60	400	s.c.	7, 9.5, 12, 15	28									2: GD 9.5–15 (esp. GD 12): more time in, and entries into, empty chamber. 3: GD 12: more time in familiar and central compartments, less time in unfamiliar compartment, more entries to familiar chamber, fewer entries to unfamiliar chamber, more locomotor activity in central and familiar chambers, less locomotor activity in unfamiliar chamber. GD 7–12: less extra time spent in unfamiliar than familiar chamber	2: GD 7, 9.5: insignificantly less time in conspecific than object chambers. 3: GD 12: insignificantly more time spent in, and entries to, centre. GD 15: more time spent with unfamiliar, again

Dev Neurosci 2020;42:12–48
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Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Kim [38], 2013	2, 3, 6	Rat	Both	36–108	400	s.c.	12	26–53				NA					2: Males: less time in, fewer entries into, conspecific chamber; more time in, more entries into, central chamber; fewer approaches to conspecific. 3: Males: more time in, and entries to, familiar and central chambers, fewer entries to unfamiliar side, more approaches to familiar, fewer approaches to unfamiliar. Both sexes: less time in unfamiliar side. Females: less time in unfamiliar side. 6: Males: hyperlocomotion, increased distance moved	2: Females: no effect. 3: NA. 6: Not significant in females
Kim [9], 2013	2, 3, 6	Rat	Males	15–30	400	s.c.	12	28–30				Total distanced moved, duration of movement					2: Less time in, fewer entries into, conspecific chamber. More time in, more entries into, object chamber. 3: More entries to familiar side, more time spent interacting with familiar. 6: Increased moving distance and duration	2, 6: NA. 3: Similar time spent in unfamiliar side
Kim [78], 2014	2, 3, 4, 6, 7	Mouse, rat	Both	20–26	300	s.c.	10	21–29, 32–34				Total distance moved, velocity					2: Less time in conspecific chamber, more time in empty chamber, less time exploring conspecific than object. 3: Fewer approaches to unfamiliar. 4: Less exploration time difference between novel and familiar objects. 6: Increased locomotor activity and velocity. 7: More marbles buried	2, 3, 4, 6, 7: NA
Kim [147], 2014	2, 3, 6	Rat	Both	8–16	400	s.c.	12	26–53				Total distance moved, duration of movement					2: Less time in conspecific chamber, more time in central chamber. 3: More time in familiar and central compartments, less time in unfamiliar compartment. 6: Increased distance moved and movement duration in field	2: Duration in object chamber: no effect. 3, 6: NA
Kim [148], 2017	2, 3, 6	Rat	Males	14–204	400	s.c.	12	26–53				Total or centre distance moved, duration in centre, total time grooming					2: Similar times in object and conspecific chambers. 3: More time with familiar than unfamiliar. 6: Increased distance moved and self-grooming	2, 3, 6: NA

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Kim [149], 2019	2, 3, 5, 6, 7	Mouse	Both	15–23	300	s.c.	10	24–35		30 min (test mouse)	Time sniffing, following, allogrooming, crawling under	Cumulative self-grooming time, repetitive digging					2: Similar times in conspecific and empty chambers. 3: No difference between times in unfamiliar and familiar chambers. 5: Decreased total social interaction. 6: Increases self-grooming and repetitive digging times, more centre time, increased distance moved. 7: Increased digging (no marbles)	2, 3, 5, 6, 7: NA
Kinjo [150], 2019	8	Rat	Males	47	100, 200	i.p.	12.5–21.5	30					Y	Spontaneous alternation			8: No differences	8: NA
Kotajima-Murakami [151], 2019	5	Mouse	Males	21–24	600	s.c.	12.5	35–42, 70–77	8–10	15 min	Active social interaction (sniffing, allogrooming, mounting, following)						5: Adolescents and adults had decreased active social interaction	5: NA
Kumar [152], 2016	2, 3, 6, 8	Rat	Males	13–15	500	i.p./s.c.	12.5	43–47				Number of beam breaks for locomotor activity. Latency to first holepoke, number of rearings and hole-pokes	Y		Spontaneous alternation	NA	2: Less time in conspecific chamber, more time in object chamber. 3: Less time in unfamiliar chamber, more time in familiar chamber. 6: Hyperlocomotion. Increased time to first holepoke, fewer holepokings and rearings. 8: Decreased spontaneous arm alteration	2, 6, 8: NA
Kumar [153], 2016	2, 3, 6, 8	Rat	Males	18	500	i.p./s.c.	12.5	44, 45				Number of beam breaks for locomotion; latency to first holepoke, numbers of holepokes and rearings for exploration	Y		Spontaneous alternation	NA	2: Less time in conspecific chamber, more time in object chamber. 3: Less time in unfamiliar chamber, more time in familiar chamber. 6: Hyperlocomotion. Increased time to first holepoke, decreased holepokes and rearings. 8: Decreased spontaneous arm alteration	2, 3, 6, 8: NA
Kumar [154], 2015	2, 3, 6, 8	Rat	Males	18	500	i.p.	12.5	43–46				Number of beam breaks for locomotion; latency to first holepoke, numbers of holepokes and rearings for exploration	Y		Spontaneous alternation	NA	2: Less time in conspecific chamber, more time in object chamber. 3: Less time in unfamiliar chamber, more time in familiar chamber. 6: PD 43: hyperlocomotion. PD 49: increased time to first holepoke, decreased holepokes and rearings. 8: Decreased spontaneous arm alteration	2, 3, 6, 8: NA

Dev Neurosci 2020;42:12–48
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Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Kumaravel [49], 2017	6	Rat	Males	12	600	i.p.	12	90				Numbers of rearings and holepokes. Peripheral and central movements, rearing/grooming					6: Decreased peripheral and central movements. Decreased rearing, self-grooming, hole-poking	6: NA
Kuo [35], 2017	1	Mouse	Males	NA	400	i.p.	11.5, 12.75, 15.5	8	NA								1: GD 12.75: decreased calls, durations, average peak frequency, peak amplitude. GD 11.5: decreased duration	1: GD 15.5: no effect
Langari [155], 2020	2,3,6	Rat	Males	16	400	i.p.	8, 9, 10	40–45				Stereotypic movement, grooming, rearing					2: Decreased sociability index. 3: Decreased social preference index. 6: Increased exploratory rearing, stereotypic grooming. Decreased distance moved, and time spent, in centre	2, 3, 6: NA
Lim [156], 2017	2, 3, 6	Mouse	Males	14–20	500	i.p.	12.5	42				Total movement, duration in centre					2: Increased centre time, less time in conspecific than object chamber. 3: More centre time, less time in unfamiliar than familiar chambers. 6: Increased thigmotaxis (less time in centre)	2: NA. 3: Total distance moved: no effect. 6: No difference in total distance moved
Lin [157], 2013	5, 6	Rat	Males	62–65	500	i.p.	12.5	28–35		"Night before"	Time following, mounting, grooming, sniffing conspecific	Percent time spent in centre, total distance moved					5: Decreased social interaction time and frequency. 6: Decreased centre time	5: NA. 6: No difference in total distance travelled
Lin [158], 2019	2	Rat	Males	10	500	i.p.	12, 13	46									2: More time in object chamber, less time in conspecific chamber	2: NA
Liu [159], 2016	5, 6	Rat	Males	20	600	i.p.	12.5	35–75		PD 35: 3.5 h. PD 75: 1 week (test mouse)	PD 35: latency to pinning, total time and frequency of pinning. PD 75: latency to social behaviour, total time and frequency of sniffing, licking, crawling/mounting, approaching/following	PD 69: intensity and duration of stereotypies. PD 71: number of rearings and hole-pokes					5: PD 35: decreased latency to, and duration of, pinning. PD 75: longer latency to social behaviour. 6: PD 69: more time in repetitive behaviours (biting, gnawing, licking). PD 71: less hole-poking	5: PD 35: no difference in pinning frequency. PD 75: no difference in frequency and duration of social behaviours (listed adjacent). 6: NA
Lucchina [160], 2014	2, 4, 6	Mouse	Males	20–60	400	s.c.	12.5	56–70				Total distance walked, number of rearings; time spent in centre, percent distance in centre					2: No effect, but less time sniffing conspecific. Less time exploring (sniffing) conspecific, similar times with both conspecific and object. 4: No effect. 6: Decreased rearings	2: Total locomotion: no effect. Still more time in conspecific chamber. 4: NA. 6: No difference in total distance walked, tie spent in centre, percent distance walked in centre

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Mahmood [161], 2018	2, 3, 5, 6, 8	Mouse	Males	16–18	600	s.c.	13	25–39		10 min (test mouse)	Frequency and total time in near and away from intruder, number of nosepokes towards intruder	PD 25: cumulative time spent self-grooming, frequency and total duration of self-grooming, circling, walking backwards. PD 35–36: total distance travelled, number of times crossing centre	T		Spontaneous alternation	NA	2: Similar times in object and conspecific chambers. 3: Similar times in familiar and unfamiliar chambers. 5: Less time with stranger, decreased duration and frequency of nose sniffs. 6: PD 25: increased self-grooming frequency, circling and backward-walking stereotypy. PD 35–36: NA. 8: More repetitive sameness	2, 3, 5: NA. 6: PD 25: NA. PD 35–36: no difference in total distance travelled, frequency of centre-crossings. 8: NA
Malyshev [64], 2013	5	Rat	Both	127	600	i.p.	12.5	29		6–16 days	Choice between mother and non-lactating female, or between sibling or stranger rat						5: More time in contact with mother than non-lactating female. Longer latency to contact mother or non-lactating female. Longer latency to socially interact with mother or non-lactating female. Fewer social groomings (with any conspecific)	5: No difference in time of social behaviour. No difference in choosing between sibling and stranger rat
Markram [162], 2007	5, 8	Rat	Both	78–274	500	i.p.	12.5	90		"Night before"	Time pinning, following, touching, grooming, sniffing (anogenital and non-anogenital) conspecific, initial hiding inside tube		Y		Spontaneous alternation	NA	5: Less pinning, non-anogenital sniffing, touching (play behaviour); more hiding. 8: More VPA rats picked same arm in successive trials	5: Grooming and anogenital sniffing: no effect. 8: NA
Matsuo [163], 2017	4, 5, 8	Rat	Males	NA	600	p.o.	12.5	50		Nil	NA		Y		No mention	NA	4: Less difference in times exploring both. 5: Less social interaction. 8: Deficits of spatial-reference memory	4, 5, 8: NA
Matsuo [164], 2020	2, 3, 4, 5, 6, 8	Rat	Males	16	600	p.o.	12.5	42–35		Nil	Time spent following, sniffing, climbing, allogrooming, and/or huddling	Self-grooming time	Y	Spontaneous alternation		NA	2: Reduced social interaction time. 3: Decreased exploration time of unfamiliar. 4: Unable to discriminate novel from familiar objects. 5: Social interaction time was reduced. 6: More time self-grooming. 8: Decreased % alternation	2, 3, 4, 5, 6, 8: NA
Mehta [165], 2011	6, 7	Mouse	Both	48	600	s.c.	13	42–71				Cumulative time self-grooming; number of centre entries, time spent in centre; total distance travelled					6: PD 42-50: more self-grooming. PD 56-64: fewer centre entries. 7: More marbles buried	6: PD 56–64: no difference in time spent in centre. No difference in baseline locomotor activity. 7: NA

Dev Neurosci 2020;42:12–48
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Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Melancia [39], 2018	1, 2, 3, 4, 5, 6	Rat	Both	33–59	500	i.p.	12.5	9, 35, 90	1	3 h	Time pinning, pouncing, partial rotation, evasion, social sniffing, play responsiveness	Number of head dippings, number of line crossings on a demarcated grid					1: Males: fewer calls. 2: Males: less time sniffing conspecific. 3: Males: less difference in time spent between familiar and unfamiliar chambers. 4: No effect. 5: Increased frequency of evasion and partial rotation to play solicitation. 6: PD 35: males had increased head dippings. PD 90: increased head dippings	1: Females: not fewer calls. 2: Females: no effect. No difference in time in object chamber. 3: Females: no effect. 4: NA. 5: General social sniffing: no effect. 6: No differences in locomotion (line crossings) on PD 35 or 90. Females did not show increased head dipping on PD 35
Mirza [166], 2019	2, 3, 6, 8	Rat	Males	18	500	i.p.	12.5	42–48	8	Nil			latency of the first poke, the number of rearing and hole-poking	Y	Spontaneous alternation		2: Decreased time spent in conspecific chamber, increased time spent in object chamber. 3: Decreased time spent in unfamiliar chamber, increased time spent in familiar chamber. 6: Decreased spontaneous alternation. 8: Increased latency to first hole-poke. Decreased number of hole-pokes and rearings	2, 3, 6, 8: NA
Mirza [167], 2019	2, 3, 6, 8	Rat	Males	12	500	i.p.	12.5	42–48	8			Latency to first poke, number of rearing and hole-pokings		Y	Spontaneous alternation		2: Decreased time in conspecific chamber. 3: Decreased time in unfamiliar chamber. 6: Increased latency to first poke. Decreased number of hole-pokings. 8: Decreased spontaneous alternation	2, 3, 6, 8: NA
Moldrich [34], 2013	1, 2, 5, 6	Mouse	Males	11–40	600	i.p.	12.5	8, 24–34	Multiple	Nil	Time nose-nose and anogenital sniffing, following, crawling, pushing	Position and rearings, distance travelled, resting time; number of grooming and digging bouts, time spent grooming and digging in each bout, total time grooming and digging (separately)					1: Decreased call frequency, call types, complex calls, 2-syllable, downward calls. More flat calls. 2: Similar time with, number of approaches towards, both object and conspecific. Fewer approaches to conspecific, less time in conspecific chamber. 5: Fewer nose-to-nose sniffings/contacts. 6: PD 25: no effect. PD 26–30: increased grooming time, more initiations of grooming, more time grooming per bout. More time digging, more initiations of digging, more time digging per bout	1: Decreases in simple calls, not different. 2: NA. 5: Both groups spent less time interacting than grooming and arena-exploring. 6: No difference in mean distance travelled, mean resting time. No other stereotypies observed
Mohammadi [168], 2020	2, 3, 6	Rat	Males	16	600	s.c.	12.5	55–57	6–10	Nil		Stereotypic grooming, distance travelled					2,3: Decreased sniffing of new conspecific. 6: Excessive grooming. Less time, and distance travelled, in centre of arena	2,3,6: NA

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Mychasiuk [53], 2012	4, 6, 8	Rat	Both	66–150	800	p.o.	12	65–75, 96–100				Total activity and distance travelled	T		Forced and food reward	No mention	4: Increased touches to new familiar object. 6: No effect. 8: More acquisition trials, more errors during acquisition time. Females: more errors than males	4: No difference in number of touches to old familiar object. 6: No difference in activity level. 8: NA
Narita [169], 2010	6	Rat	Males	15	800	p.o.	9	105				Central, peripheral, total ambulatory distance					6: Increased distance moved	6: No effect on preference for centre over peripheral corners
Olexova [67], 2013	6	Rat	Both	36	600	i.p.	12.5	21, 42, 72				Locomotor activity (horizontal and vertical beam breaks) and habituation					6: PD 42, 72: gradually decreased locomotion, quicker habituation, decreased exploration intensity, increased exploration rapidity	6: No locomotor changes between ontogenetic stages, as opposed to controls. PD 21: no locomotor/habituation differences
Olexova [170], 2016	6	Rat	Both	36	600	i.p.	12.5	72				Percent activity in inner and outer zones, and total activity (number of beam breaks)					6: More activity in outer zone, less in inner zone. Overall increased activity	6: NA
Olde Loohuis [171], 2015	5, 6	Rat	Both	179	495	i.p.	12.5	30–35, 42–46		3.5 h	NA	Movement and location					5: Decreased pinning time, increased non-social behaviour time. 6: No effect in activity/exploration	5: NA. 6: No different in durations in different areas of the field or self-assigned "home base"
Peralta [172], 2016	2, 6, 8	Rat	Males	13–15	450	i.p.	12.5	30				Total distance travelled, mean speed, duration and frequency of grooming	Y		Forced	NA	2: Similar time in all 3 chambers. 6: Decreased total distance and mean speed, increased frequency and duration of self-grooming. 8: Reversal phase: increased re-entries, time in the novel arm	2, 6, 8: NA
Qin [173], 2016	2, 3, 6	Rat	Males	20	400	i.p.	12.5	33–35				Movement and time spent in centre and in self-grooming					2: Less/equal time in conspecific than/as object chamber. 3: Not more time spent in unfamiliar than familiar chambers. 6: Longer distances travelled, increased self-grooming rates	2, 3, 6: NA
Rajizadeh [174], 2019	2, 3	Rat	Males	20	600	i.p.	12.5	21–51									2: Less tendency toward conspecific. 3: Less tendency toward unfamiliar	2: NA 3: NA
Raza [46], 2015	5	Rat	Both	32	800	p.o.	12.5	29–34		24 h	Play: attacks and defences (incl. complete and partial rotations), pinnings. Mountings. Stress: frequencies of head/body shaking, scratching, stereotyped grooming						5: Decreased supine defensive tactics, increased standing defence tactics, more mounting, more head and body shakes, fewer play-initiation calls (esp. in 5th min.), more initiations of playful attacks in first 3 min	5: Frequency of nape attacks/defences (incl. evasions) or pinnings, probability of partial rotations, scratching/allogrooming: no effect

Dev Neurosci 2020;42:12–48
DOI: 10.1159/000509109

Table 1 (continued)

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Raza [54], 2015	6, 8	Rat	Both	151	800	p.o.	12.5	65, 75, 96				Activity and distance travelled	T		Forced and food reward	No mention	6: Hyperlocomotion in both sexes, significant in male. 8: Males: more days to reach criterion	6: Almost significant increase of activity in females. 8: Females: insignificant trend towards more days to reach criterion
Roullet [42], 2010	2, 3, 6	Mouse	Both	79	800	p.o.	11	22–25				Basic movements, vertical and horizontal ambulations					2: Similar numbers of nosepokes towards both conspecific and object sides. 3: Less exploration (fewer nosepokes) of both unfamiliar and familiar. 6: No effect	2: NA. 3: Still no more time with unfamiliar over familiar. 6: No difference in locomotor activity
Sakade [175], 2019	2, 6	Mouse	Males	35	400	i.p.	14	56–63				Number of entries into centre, time spent in centre					2: No preference towards conspecific chamber. 6: More entries and time spent in centre, but likely due to concurrent hyperactivity	2, 6: NA
Sandhya [176], 2012	5, 6	Rat	Males	12–20	600	i.p.	12.5	30–40, 90–110		"Night before"	Both age groups: frequency of pinning, following, touching, grooming, anogenital and non-anogenital sniffing. Only adults: initial time hiding inside tube	Number of photobeam breaks for locomotion, numbers of rearings and holepokes for exploration					5: PD 30–40, 90–110: fewer social explorations (pinning, sniffing, grooming, following, climbing, anogenital inspections). 6: Hyperlocomotion, decreased rearing and holepoking	5, 6: NA
Servadio [62], 2015	1	Rat	Both	NA	500	i.p.	12	5, 9, 13	NA								1: PD 5, 9; males: fewer calls	1: Call shape not altered. PD 13: no effect. Females: no effect
Servadio [177], 2016	1, 2, 5, 6	Rat	Males	30–46	500	i.p.	12.5	9, 35, 90	1	3 h	Play responsiveness	Number of hole-dippings					1: Fewer calls. 2: Less time exploring conspecific. 5: PD 35: less play responsiveness. 6: Increased stereotypic head dippings	1: No differences in percentage of different call categories. 2: Total number of entries: no effect. 5: NA. 6: NA
Servadio [66], 2018	1, 5	Rat	Males	29-98	350, 400, 500	i.p.	12.5	5, 9, 35, 90	1	24 h for adults, 3 h for pups	PD 35: frequencies of pinning, pouncing, evasion, play responsiveness; time sniffing/grooming. PD 90: frequency and time of sniffing/grooming/licking; mean duration of these behaviours						1: 400, 500 mg/kg, PD 9: fewer calls. 5: PD 35, 500 mg/kg: more social-contact avoidance, fewer responses to play solicitation. PD 90, 500 mg/kg: reduced mean social-exploration time	1: PD 5: no effect. 350 mg/kg: no effect. 5: 350, 400 mg/kg: no effect. PD 35, general social exploration: no effect. PD 90: NA
Servadio [178], 2016	2, 5	Rat	Males	NA	500	i.p.	12	30–35, 70–80		Nil	NA						2: Less time approaching conspecific. 5: Fewer responses to play solicitation	2, 5: NA

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Schiavi [208], 2019	2, 3, 5	Rat	Males	16–18	500	i.p.	12.5	35–40, 90–95	8	3 h for social play, 1 week for 3-chamber	Number of pinnings and pouncings, evasion, play responsiveness, time spent sniffing or allogrooming						2: Less time sniffing conspecific. 3: Lower discrimination index. 5: Reduced play responsiveness, more partial rotations	2,3: NA. 5: No differences in pinning, pouncing or total time interacting
Schneider [56], 2008	5, 6	Rat	Both	16–32	600	i.p.	12.5	90–150		1 week	Latency to, and frequency of, sniffing/licking, crawling/ mounting, approaching/ following	Breakage of beams for locomotor activity, repetitive breaking for stereotypy					5: Males: more time to social behaviour, fewer social explorations. Females: decreased explorations, longer latency to these behaviours. 6: Males: increased time and number of stereotypies in 40–60 min. Females: increased time and number of stereotypies in 1st 40 min, number in 40–60 min	5: Latency to social behaviour, number of social explorations: no effect. 6: NA
Schneider [57], 2005	5, 6	Rat	Males	16–47	600	i.p.	12.5	30–50, 90–120		3.5 h	PD 30–50: latency to pinning, total time and frequency of pinning; latency to following/ approaching, mounting/ crawling, sniffing/ grooming, their durations and frequencies. PD 90–120: latency to, frequency and duration of, non-anogenital and anogenital sniffing/licking, crawling/ mounting, approaching/ following	Breakage of photobeams for locomotor activity, repeated breakage of 3 beams for stereotypy, number of rearings and holepokes for exploratory activity					5: PD 30–50: fewer pinnings. PD 90–120: fewer social explorations, longer time to social behaviour. 6: Increased locomotion and stereotypy (duration, frequency), decreased exploration (rearing, holepoking). Adults: more stereotypy, differences later than adolescents. Females: earlier increased locomotion and stereotypy	5: PD 30–50: no difference in latency to, and time of, pinning; time of, social non-play behaviours (listed adjacent). Insignificant longer latency to social non-play behaviour. PD 90–120: no difference in time or sum of social explorations and anogenital inspections, nor number of anogenital inspections. 6: Insignificant increased stereotypy in 1st 10 min, in adolescents
Schneider [179], 2007	4	Rat	Males	16	600	i.p.	12.5	60–90									4: No effect	4: Both groups spent more time exploring novel object
Schneider [180], 2004	5	Rat	Males	22	600	i.p.	12.5	30–50, 90–120		3.5 h	Latency to, time and frequency of pinning. Latency to, time and frequency of, following/ approaching, mounting/ crawling, sniffing/ grooming. Non-anogenital and anogenital sniffing/licking						5: PD 30–50: decreased pinning frequency. PD 90–120: more time to social behaviour, fewer social explorations	5:No difference in latency to, time of, pinning; latency to, and time of, following/ approaching, mounting/ crawling, sniffing/grooming. Latency to these were insignificantly longer. In adults, no difference in times of social behaviours, sum of social explorations and anogenital inspections, or number of anogenital inspections

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Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Stefanik [181], 2015	2	Rat	Both	36	600	i.p.	12.5	25, 46, 76									2: More time in conspecific chamber, less time in central chamber, quicker to initiate direct interactions with conspecific. Males: more active in object chamber than were females. Age effect: time in central chamber, time to start social interaction, decreased over time; time in object chamber, entries into all 3 chambers, increased over time; less time sniffing empty cage at weaning, than at puberty/adulthood	2: Control females spent less time interacting with conspecific. Time spent in object side, time sniffing the object or entries into the chambers: no effect
Tartaglione [58], 2019	1, 6	Mouse	Both	28–40	500	s.c.	10.5	4–12	NA			Frequencies and durations of locomotion, head rising, face-washing, wall-climbing, curling					1: Paternal lineage: lower call frequency. PD 10: females: shorter call durations. 6: F1: more time in locomotion; VPA females had more head risings. F2: paternal lineages had longer curling durations. F2, F3: both lineages spent more time in locomotion, esp. PD 7: more head risings. Longer wall-climbing durations in maternal lineage (PD 7–12)	1: Call number/amplitude: no effect. Other PDs: no effect. 6: VPA males did not have a higher frequency of head rising. No sex differences in F2, F3. F2, F3: insignificant increase of face-washing in maternal lineage. F3: insignificant difference between maternal-lineage VPA and controls in time spent in locomotion
Takuma [182], 2014	4	Mouse	Males	80	500	i.p.	12.5	63									4: Decreased difference between exploratory times for novel vs. familiar objects, 24 h later	4: No difference, 1 h later
Tian [183], 2014	3, 4, 6	Rat	Males	8–12	600	i.p.	12.5	50				Locomotion					3: Less social interaction, no difference in times spent between unfamiliar and familiar chambers. 4: Decreased difference in time exploring novel and familiar objects. 6: No effect	3, 4: NA. 6: Normal daytime locomotor activity and duration
Tsuji [184], 2020	1	Mouse	Both	14–25	400	i.p.	12.5	3–14									1: No USV peaks in either males or females. Lower calls on PD 11, in both sexes	1: NA
Tsujino [185], 2007	6	Rat	Both	68	800	p.o.	9	18				Number of grid-line crossings					6: More grid-line crossings. Greater locomotor activity in light phase	6: Both groups showed greater locomotor activity in dark than light phases. No difference in locomotor activity in the dark phase
Tyzio [186], 2014	1	Rat	Both	44	600	i.p.	12	4	NA								1: Fewer calls, shorter total call durations	1: NA
Wagner [187], 2006	6	Mouse	Both	70	200, once daily; 600	s.c.	12–17	22–26				Habituation, motor activity					6: PD 23, females: hyperlocomotion, within-bout habituation	6: No difference in males

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Wang [188], 2018	2, 3	Mouse	Males	15	500	i.p.	10.5	NA									2: Similar times in conspecific and object chambers. 3: No more time in unfamiliar than familiar chambers	2, 3: NA
Wang [189], 2018	2, 3, 6, 7	Mouse	Males	12–16	600	i.p.	12.5	30, 56				Total distance travelled					2: Less time interacting with conspecific. 3: Less increase in time spent in unfamiliar over familiar chambers. 6: Longer travelling distance. 7: More marbles buried	2, 3, 6, 7: NA
Wang [190], 2013	5	Rat	Males	24	500	i.p.	12.5	28–35		"Night before"	Time following, mounting, grooming, sniffing						5: Decreased time and frequency of social interaction	5: NA
Wang [191], 2018	5, 6, 7	Mouse	Males	16	600	i.p.	12.5	31–35		Nil	Time in social zone, sniffing conspecific; average distance travelled	Duration of self-grooming, time spent in centre, total distance travelled					5: Lower social-interaction time. 6: Increased time spent grooming, decreased time spent in centre. 7: More marbles buried	5: Mean distance travelled: no effect. 6, 7: NA
Wang [192], 2018	6	Rat	Males	15	400	s.c.	12.5	56				Duration of self-grooming					6: Increased self-grooming time (in novel environment)	6: NA
Wang [193], 2019	2, 3, 6, 8	Rat	Males	20	500	i.p.	12.5	42–56				Total number of of times rats crossed arena, number of times rats crossed middle square (exploratory)	Y	Spontaneous alternation			2, 3: Spent time equally in both chambers. 6: Less time in central region. 8: Lower spontaneous alternation rate	2, 3, 6, 8: NA
Wei [68], 2016	4, 6	Mouse	Both	80	100, 200	s.c.	17	35–48, 84–105				Distance travelled, centre distance travelled					4: PD 84–105, 200 mg/kg: similar times exploring novel and familiar objects. 6: No effect	4: PD 35–42: no effect. 6: NA. NB: Adults were more active than juveniles, across all treatment groups
Wellmann [194], 2014	5	Rat	Both	32–48	200, half-daily	i.p.	12, 12.5, 13	40–45		30 min	Play (pinning, pouncing, nape attacks, chasing), following, sniffing, crawling, grooming, crossovers to/from conspecific						5: Males: more play fighting contact and investigation, dose-dependently	5: Females: no effect
Win-Shwe [195], 2018	2, 3	Rat	Both	32	600	i.p.	12.5	77–91									2: Similar times in conspecific and object chambers. 3: More time in familiar than unfamiliar chambers	2, 3: NA
Wu [70], 2017	2, 3	Rat	Males	8–16	600	i.p.	12.5	35–50									2: PD 35, 50: similar times in both object and conspecific chambers, less time exploring conspecific. 3: Less time sniffing unfamiliar	2, 3: NA

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Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Wu [196], 2017	2, 5, 6, 7	Rat	Both	24	500	i.p.	12.5	28–42		Nil	Time sniffing, mounting, following, crawling under	Duration in each demarcated square and central zone					2: Less time in conspecific chamber, more time in object chamber. 5: Less sniffing and following. 6: Decreased centre time. 7: More marbles buried	2, 6, 7: NA. 5: Mounting or crawling under: no effect
Wu [197], 2017	7	Rat	Males	NA	500	i.p.	12.5	28–35									7: More marbles buried	7: NA
Wu [198], 2018	2, 6	Rat	Males	14–16	500	NA	12.5	28–35				Total distance travelled					2: No more time in conspecific than object chambers. 6: Hyperlocomotion (increased distance travelled)	2, 6: NA
Yamaguchi [199], 2017	4, 5, 6	Mouse	Males	12–64	500	i.p.	12.5	28, 56, 57		60 min	Time face and anogenital sniffing	Total distance travelled, rearings, entries into centre					4: Less time exploring novel object. 5: Decreased sniffing time. 6: Decreased locomotion, rearings, centre entries	4: No difference in total exploration time. 5, 6: NA
Yoshikawa [200], 2017	2	Mouse	Males	NA	300, 400	i.p.	10–12	NA									2: No more time in conspecific than object chambers	2: NA
Zamberletti [201], 2019	2, 3, 4, 6	Rat	Both	13–24	500	i.p.	12.5	30–58				Repetitive behaviours (compulsive self-grooming)					2: Less time in conspecific chamber. 3: Similar times exploring familiar and unfamiliar 4: Decreased discrimination index 6: Increased time spent by male rats, compulsively self-grooming	2, 3, 4: NA. 6: Female rats unaffected
Zhang [52], 2015	6	Rat	Both	NA	600	i.p.	12.5	"Adolescent"				Changes in mean activity, duration of self-grooming, number of rearings					6: Hyperactive at 20–25 min. increased distance travelled at 0–10 and 20–25 min. More time in self-grooming activities. More rearing episodes	6: Insignificant hyperactivity at 0–15 min
Zhang [202], 2018	2	Rat	Males	18	600	i.p.	12.5	30–35									2: Fewer entries to, less time in, conspecific chamber	2: NA
Zhang [203], 2017	5, 6	Rat	Both	16–20	600	i.p.	12.5	7, 9, 14, 21, 35		3.5 h	Frequency and time of chasing and physical contact	Straight times, duration of grooming					5: Decreased frequency and time of social behaviour, travelling straight; increased grooming frequency. 6: Increased self-grooming frequency, decreased times travelling straight	5, 6: NA
Zhang [204], 2017	6	Rat	Males	18	600	i.p.	12.5	23				Mean activity, repetitive movements					6: More time in (1st 40 min), and number of, repetitive/ stereotypic activities. Increased distance travelled at 0–40 and 50–60 min	6: NA

Table 1 (continued)

First author [Ref.], year	Tests performed	Species	Sex	Sample size	Dose, mg/kg	Route	Treatment age (GD)	Testing age (PD)	Offspring per mother, *n*	Social restriction time	Measured social interaction behaviours	Measured open field behaviours	T/Y maze	Spontaneous alternation or rewarded/ forced version	Food in rewarded maze	Food restriction time	Test and positive results	Test and negative results
Zhang [205], 2012	6	Rat	Males	NA	600	i.p.	12.5	"Adolescent"				Changes in mean activity level, for stereotypies					6: Increased frequency and duration of stereotypy in 1st 20 min, hyperlocomotive and higher-frequency stereotypy in 2nd 20 min More distance travelled in 3rd 20 min	6: NA
Zhang [206], 2019	2, 3, 6	Rat	Males	20	600	i.p.	12.5	23–45				Movement and time spent in each region, frequency and duration time of self-grooming					2: Less time in conspecific chamber, more time in object chamber. 3: spent equal amounts of time in familiar and unfamiliar chambers. 6: Less time in, and entering, centre. Increased self-grooming time and frequency	2,3: NA. 6: No difference in total travel distance
Zhao [40], 2015	2, 3	Rat	Both	20	600	i.p.	12.5	31									2: Less time exploring conspecific, more time exploring object. Males: less time in conspecific chamber, fewer explorations of conspecific, more explorations of object, than in females. 3: More time exploring familiar, less time exploring unfamiliar. Males: less time in unfamiliar side than females, higher frequency exploring familiar, lower frequency exploring unfamiliar, higher frequency exploring familiar than females	2: Females: not as decreased time with conspecific, not as increased frequency exploring object. 3: In females: time exploring familiar, not as much as in males

Tests performed: 1, ultrasonic vocalisation test; 2, social preference test; 3, social novelty preference test; 4, novel object recognition test; 5, social interaction test; 6, open field test; 7, marble burying test; 8, T/Y-maze test. Each study is shown alongside the ASD tests, the investigators performed, the species, sex and sample size of the rodents tested, the dose and route (mode of injection) used, the ages the rodents were treated and tested at, the number of offspring used per mother for ultrasonic-vocalisation tests, social restriction time before social tests, the parameters measured in social interaction and open field tests, whether T- or Y-shaped mazes were used for alternation tests, the mode of alternation test used, along with the food used and food-restriction times before testing. Finally, positive and negative results of all tests are listed after the numbers for the tests used in each study. Positive results were behavioural differences in the rodents, compared to control rodents; negative results were where there were no differences between control and treatment rodents. i.p., intraperitoneal mode of injection; s.c., subcutaneous mode of injection; p.o., oral route of ingestion; GD, gestational day; PD, postnatal day.

Table 2. Search strategy in each database

Database	Search protocol	Initial number of records
ProQuest	((autis* OR ASD OR "pervasive development* disorder*") AND (rat OR mouse OR rodent OR mice) AND (behav* or charact* or respons*)) AND MJMESH.EXACT("Valproic Acid")	143
PsychInfo	1. (autis* or ASD or "pervasive development* disorder*").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 2. exp Autism Spectrum Disorders/ 3. 1 and 2 4. (rat or mouse or rodent or mice).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 5. (behav* or charact* or respons*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 6. exp Valproic Acid/ 7. 3 and 4 and 5 and 6	66
Scopus	(TITLE-ABS-KEY ((autis* OR asd OR "pervasive development* disorder*")) AND TITLE-ABS-KEY ((at OR mouse OR rodent OR mice)) AND TITLE-ABS-KEY ((behav* OR charact* OR respons*)) AND TITLE-ABS-KEY (("Valproic acid")))	350
Medline	1. (autis* or ASD or "pervasive development* disorder*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 2. exp Autistic Disorder/ 3. 1 or 2 4. (rat or mouse or rodent or mice).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 5. exp Valproic Acid/ 6. (behav* or charact* or respons*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 7. 3 and 4 and 5 and 6	164
Web of Science	1. ALL=(autis* or ASD or "pervasive development* disorder*") 2. ALL=(rat OR mouse OR rodent OR mice) 3. ALL=(behav* or charact* or respons*) 4. ALL=("Valproic acid") 5. #4 AND #3 AND #2 AND #1	351
PubMed	(((((autis* OR ASD OR "pervasive development* disorder*"))) AND ((rat OR mouse OR rodent or mice))) AND ((behav* or charact* or respons*))) AND ("Valproic acid")	271

The database is shown alongside the search protocol and the initial number of rodent studies retrieved from the database.

ence; (3) social novelty preference; (4) social interaction tests; for repetitive behaviours, (5) open field; (6) marble burying; and for cognitive rigidity, (7) T/Y maze. We have also included (8) a novel object recognition test to see whether impairments in social discrimination also extend to the non-social domain. This review places no limits on the age of the rats/mice. The inclusion criteria consisted of: (1) behaviours core to ASD as specified, (2) behavioural experiments on mice and rats, (3) the use of prenatal exposure to VPA, and (4) English-language articles. Studies were excluded if they (1) only assessed the accessory behaviours of ASD and behaviours not related to ASD, (2) behaviours caused by agents other than VPA, (3) used postnatal VPA administration. Accessory behaviours are defined as those behavioural characteristics common to ASD individuals, but not essential to a clinical diagnosis of ASD. Identification of relevant articles was undertaken by 2 authors who cross-checked all included articles. The study process is outlined via the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, illustrated in Figure 1.

Data Extraction and Synthesis

Data extracted included species, sex, sample size, dosage (route, quantity, timing, and frequency), gestational timing of exposure, testing ages, and outcomes relative to controls. Table 1 provides information on behavioural outcomes of VPA, and Table 3 reports on studies that have attempted to alleviate VPA-induced alterations of behaviour through various drug treatments administered after birth. In this review, dosage schedules have been categorised as singular (only one dose for the subjects) and chronic (multiple doses for a subject); though it is worth noting that some papers use the term, "sub-chronic," to indicate multiple doses.

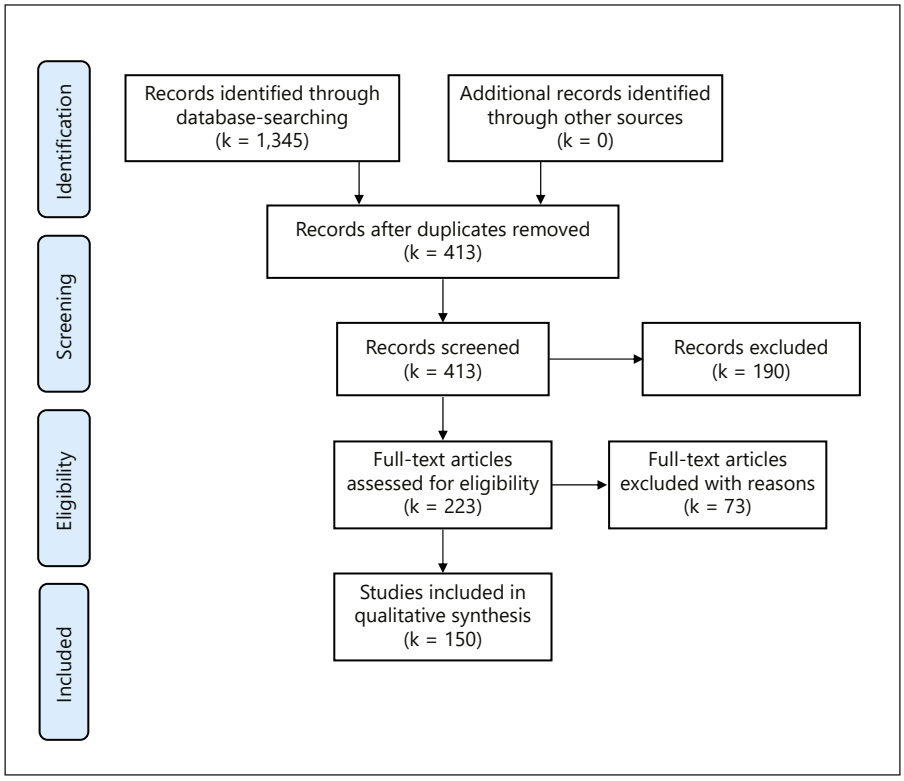

Fig. 1. PRISMA flowchart. Shown are the study numbers used in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines used for this study.

Results

Search Results (Fig. 1)

A total of 1,345 records were retrieved from ProQuest (k = 143), PsycInfo (k = 66), Scopus (k = 350), Medline (k = 164), Web of Science (k = 351), and PubMed (k = 271). Following duplicate removal, 413 articles remained and were screened at the title and abstract level, resulting in the exclusion of a further 190 articles. The remaining 223 articles were then retrieved and reviewed at the full-text level. A further 73 articles were excluded due to postnatal delivery of VPA, reporting on behaviours not core to ASD, and non-rodent animals tested. This resulted in a total of 150 studies being included in this review.

Core ASD Behaviour 1: Social Impairment

Four major standard tests assessing social behaviours in rodents were identified: ultrasonic vocalisation test, social preference test, social novelty preference test, and social interaction test [28–30].

Ultrasonic Vocalisation Tests

In 16 studies, VPA was delivered gestationally, and the vocalisation abilities of pups upon maternal separation were then measured (Table 1). All studies reported a reduction in ultrasonic vocalization emission by pups (both frequency and/or duration) by a singular subcutaneous (s.c.) or intraperitoneal (i.p.) injection of 400–600 mg/kg VPA on GD (gestational day) 11.5–13 (Table 1). One study administered 500 mg/kg VPA (per os; p.o.) daily between GD 11 and 13, and also found shorter calls which were more apparent in VPA females. However, these offspring demonstrated an increase in call frequency from both VPA sexes [31], in contrast to the other studies which showed decreased call frequency (Table 1). Other impairments include a deviation from the normal sound characteristics of each call type, in that calls had a lower amplitude, there were more flat calls, altered number of complex and downward calls, less variety of call types, and fewer 2-syllable calls [32–35].

Object-Conspecific Tests

Eighty studies assessed the social preference test in VPA offspring (Table 1). Taken together, the studies show that 300–600 mg/kg VPA administered between GD 9.5 and 15 (via s.c. or i.p.) reduces a rodent's preference to spend more time with a conspecific than an inanimate object (or empty cage; Table 1). Any combina-

tions of decreased time in or entries into the social chamber, and/or increased time in or entries into the object chamber show reduced social preference in VPA rodents.

The sex of the rodents influences behavioural outcomes in studies that consisted of both males and females. VPA exposure appeared to have no effect or a lesser effect in females [36–40], indicating females possess some resistance to social impairment induced by VPA, as opposed to males [41].

The oral route was also effective at a higher dose (500–800 mg/kg) to reduce preference between object and conspecific in terms of exploratory behaviours such as nose pokes, and reduce entries towards, or time with, the conspecific (500–800 mg/kg) [31, 42, 43].

Social Novelty Preference Tests

We found 51 studies indicating that 300–600 mg/kg VPA dosage (although less so at 300–450 mg/kg than 500–600 mg/kg), given between GD 10–13, reduces a rodent's preference to spend more time with an unfamiliar relative to a familiar conspecific (Table 1). This occurs by any combination of decreased time in or entries into the unfamiliar chamber, or increased time in or entries into the familiar chamber, or both. The oral route is also effective to reduce social exploration with an increased VPA dose (500–800 mg/kg) [31, 42]. One study, Melancia et al. [39], used a slightly different protocol whereby the social novelty preference test was conducted in an open field set-up (i.e., no separate chambers), and found a similar effect to the more conventional protocol (Table 1).

Novel Object Recognition Tests

Nineteen studies evaluated the novel object recognition test in animals exposed to VPA during gestation (Table 1). The studies show that 200–600 mg/kg VPA given i.p. between GD 10 and 12.5 reduced the discrimination index between both objects, such that VPA-exposed rodents spent relatively more time exploring the familiar than the novel object (Table 1). Overall, a substantial variability is widely reported with regard to the influence and derived different phenotypes of the VPA model [44, 45]. Probably, some conflicting results in the current literature are linked to the different ranges of VPA dosage used in the various experimental procedures.

Social Interaction Tests

Forty-eight studies investigated the effect of gestational VPA exposure on the social interaction test (Table 1). The results show that social interaction is impaired when 400–600 mg/kg VPA is administered on GD 11.5–12.5 (i.p. or s.c.; Table 1). An oral dose of 800 mg/kg of VPA seems to have a similar effect [46]. At lower doses (350 mg/kg or less), social behavioural impairments were less prominent. Duration of social restriction, before testing, ranged from 5 min [47] to 9 weeks [48], and did not seem to make a noticeable difference to the social interactions between the 2 conspecifics. Definitions of specific behaviours are given in Table 3.

To summarise the social behavioural tests, synthesis of the findings suggests a number of deficits in the VPA offspring, compared to control offspring: ultrasonic vocalization calls are impaired; there is decreased preference to spend time with a conspecific over an object, or an unfamiliar conspecific over a familiar; and social one-to-one interaction is impaired.

Core ASD Behaviour 2: Repetitive Behaviours

Open Field Tests

We found 83 studies that delivered VPA gestationally and showed the open field test results (Table 1). Taken together, the results show that when 400–600 mg/kg (especially towards the higher doses) of VPA is administered between GD 11.5 and 13.5 (i.p. or s.c.), stereotypies increase in the rodent offspring (Table 1).

Repetitive behaviours were also observed at the lower doses. Specifically, stereotypic self-grooming, digging, jumping, and headshakes were increased at 300–600 mg/kg VPA (Table 1; although self-grooming and hole-poking were decreased in one study [49]). Interestingly, Jaiswal [50] showed increased self-grooming with the very low doses of 25 and 50 mg/kg VPA. In addition, Kang and Kim [51] found that a novel bright environment induced stereotypies, whereas a dark familiar environment did not. It was proposed that the bright environments may increase anxiety in rodents, contributing to ASD-related stereotypies. In terms of exploratory behaviour, rearings decreased at 400–600 mg/kg (i.p. or s.c.; Table 1), except in one study where it increased [52]. No changed parameters were seen to cause this [52]. Locomotion gave mixed results across the doses, with some having increased locomotion (hyperlocomotion), others having decreased locomotion (hypolocomotion; Table 1).

Marble Burying Tests

Fifteen studies (in which VPA was administered gestationally) used the marble burying test (Table 1). Exposure to 300–600 mg/kg VPA between GD 10 and 13 (i.p. or s.c.) increased marble burying compared to controls (Table 1). Earlier or later administrations of VPA produced either no effect (GD 13.5) [51] or the opposite effect (GD 8.5) [48].

Table 3. Definitions of specific physical interactions in the social interaction test

Behaviour	Definition	Type
Anogenital sniffing	The rodent sniffing the anogenital areas of the conspecific	Social investigative (neither friendly nor hostile)
Crawling/mounting	The rodent crawling over the conspecific	Prosocial
Digging	The rodent digging a hole into the bedding of the apparatus	Compulsive/repetitive/anxious
Fighting	Fighting in adults (approximately PD 90–120 [176, 180])	Hostile
Non-anogenital sniffing	The rodent sniffing the non-anogenital areas of the conspecific	Prosocial investigative (friendly)
Pinning	The rodent standing over the conspecific which lies flat on its back	Prosocial
Play fighting	Fighting in juveniles (approximately PD 30–50 [176, 180])	Prosocial
Play responsiveness	The probability of being pinned in response to being pounced on	Prosocial
Rearing	The rodent standing up on its hind legs	Environmentally investigative

Each behaviour is shown alongside its literal definition and the type of social behaviour it is classified as. PD, postnatal day.

Core ASD Behaviour 3: Cognitive Rigidity

Y/T-Maze Tests

Twenty studies on rodents exposed to VPA during gestation reported Y-/T-maze behaviour (Table 1). The results show that 400–600 mg/kg VPA administered between GD 11.5 and 13 (i.p. or s.c.) decreased spontaneous arm alternations (Table 1). When food was used to a-priori reinforce a particular arm, oral administration of 800 mg/kg VPA impaired initial training, with sex effects evident amongst studies: VPA-exposed females made more errors than VPA-exposed males, but VPA-exposed males required more time to learn the behaviour [53, 54].

Pilot Studies of Potential Treatment Drugs

Some studies attempted to treat VPA-induced deficits with a variety of potential pharmacotherapies (Table 4). The most commonly studied compounds can be classed as neurohormones/peptides or antioxidants/anti-inflammatories, and these alleviate at least one of the core ASD impairments (Table 4). In contrast, antipsychotics were not so effective (Table 4). Cannabinoids, cholinergics, glutamatergics, growth factors, and psychostimulants/catecholamines have also been investigated, but too few to ascertain their efficacies (Table 4).

Discussion

The evidence reviewed here consistently demonstrates that gestational exposure of 400–600 mg/kg (i.p. or s.c.) of VPA in rodents at around GD 11.5–12.5 has substantial disruptive effects on rodent-equivalent measures of the 3 core behavioural traits characteristic of ASD: reductions in social behaviours, increases in repetitive behaviours, and increases in behaviours reflecting cognitive rigidity. Similar effects were found across rodent species, indicating that both mice and rats can be used for the investigation of novel pharmacotherapies. Interestingly, there were a number of sex differences and age-of-testing effects noted that can inform future VPA-model studies (detailed below). Finally, a wide array of compounds has been assessed, and, with a few exceptions, have been found to alleviate some aspect of ASD-relevant behaviour. This result suggests possible publication bias. It is also worth noting that some papers use GD 0 as the day of conception, whereas others use GD 1. This discrepancy is negligible, since the window of neural-tube closure occurs at different times around GD 12.5 in different rodents. Therefore, there can be a ±1-day uncertainty around GD 12.5.

Core Behavioural Impairments

Gestational VPA reliably alters behaviour in a way that might be considered consistent with an ASD-like phenotype. Alterations to each of the 3 core behavioural traits were observed using multiple behavioural assays, strengthening the validity of the model. Some inconsistencies across the studies were noted, however, relating specifically to the operationalisation of target behaviours in certain tasks. The ultrasonic vocalisation, social preference, social novelty preference, social interaction, and open field tests each possess multiple possible outcome measures to characterise behaviour, and not all measures were reported in each study. For example, in the social interaction test, the following behaviours were assessed: approaches, following/chasing, sitting adjacently, pinning, mounting/crawling over, pouncing, play-fighting, nape attacks, general sniffing, face sniffing, anogenital

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Table 4. Potential treatments trialled by individual studies using VPA to first induce ASD symptoms in rodents

Drug class	Drug	First author [Ref.], year	Drug dose, mg/kg	Drug route	Treatment timing	Alleviation of social impairments	Alleviation of repetitive stereotypies	Alleviation of cognitive rigidity/inflexibility
Antioxidants/ anti-inflammatories	*Bacopa monnieri* (L.) Wettst	Sandhya [176], 2012	300	p.o.	Daily for 15 days	Y	N	Y
	Epigallocatechin	Kumaravel [49], 2017	2	p.o.	Once daily over 70 days	N	N	N
	Fingolimod	Wu [70], 2017	0.25, 0.5, 1	p.o.	Once daily over 6 days	Y	N	N
	Gastrodin	Wang [191], 2018	100	i.g.	Once daily for 15 days	Y	Y	N
	Hesperetin; nano-hesperetin	Khalaj [144], 2018	10; 20	p.o.	Once daily until end of lactation	Y	Y	N
	Hydrogen-rich water	Guo [131], 2018	1.8 mg/L	p.o.	Uncontrolled	Y	N	N
	Korean red ginseng	Kim [9], 2013	20, 50, 100, 200	p.o.	Once daily over 6 days	Y	N	N
	Korean red ginseng	Gonzales [10], 2016	100, 200	p.o.	Once daily over 20 days	Y	Y	Y
	N-acetylcysteine	Zhang [204], 2017	150	i.p.	Once daily for 4 weeks	N	Y	N
	Palmitoylethanolamide; luteolin	Bertolino [207], 2017	1	p.o.	Once daily for 2 weeks	Y	N	N
	Purple rice and silkworm pupae	Morakotsriwan [11], 2016	50, 100, 200	s.c.	Once daily over 27 days	Y	N	N
	Resveratrol	Bambini-Junior [101], 2014	3.6	s.c.	Once daily over 13 days	Y	N	N
	Sulindac	Zhang [52], 2015	5	i.p.	Acute	N	Y	N
	Sulindac	Zhang [205], 2012	5	Gestational i.p.	Acute	N	Y	N
Antipsychotics	Aripiprazole	Hara [75], 2017	3	i.p.	Acute; once daily over 2 weeks	Y	N	N
	Haloperidol	Hara [75], 2017	0.1	i.p.	Acute; once daily over 2 weeks	N	N	N
	Risperidone	Hara [75], 2017	0.2	i.p.	Acute; once daily over 2 weeks	Y	N	N
Cannabinoids	Anandamide	Servadio [177], 2016	1, 2, 2.5	i.p.	Acute	Y	Y	N
Cholinergics	Donepezil	Kim [78], 2014	0.3	i.p.	Once daily over 27 days	Y	Y	Y
Glutamatergic drugs (NMDA types)	Memantine	Kang [51], 2015	10	i.p.	Acute	Y	Y	N
	Memantine	Kumar [152], 2016	10, 20	p.o.	Once daily over 2 weeks	Y	N	Y
Growth factors	Cerebrolysin	Cuevas-Olguin [115], 2017	2.5 mL/kg	i.p.	Daily for 15 days	Y	N	Y
	Human adipose-derived stem cells	Ha [132], 2017	2 μL × 50,000 cells	i.c.	Acute	Y	Y	N
	Zinc	Cezar [108], 2018	2	Gestational s.c.	Acute	Y	N	N

Table 4 (continued)

Drug class	Drug	First author [Ref.], year	Drug dose, mg/kg	Drug route	Treatment timing	Alleviation of social impairments	Alleviation of repetitive stereotypies	Alleviation of cognitive rigidity/inflexibility
Neurohormones/peptides	Agmatine	Kim [148], 2017	25, 50, 100	i.p.	Acute	Y	Y	N
	Agomelatine	Kumar [154], 2015	2, 4	p.o.	Daily for 30 days	Y	N	N
	Atomoxetine	Choi [111], 2014	3	i.p.	Acute	N	Y	N
	Atomoxetine	Hara [134], 2016	1	i.p.	Acute; once daily over 2 weeks	Y	N	N
	Bumatenide	Liu [159], 2016	2	NA	Daily for 15 days	Y	N	N
	CP465022	Kim [149], 2019	0.25, 0.5, 1	i.p.	Acute	Y	N	N
	D-cycloserine	Wellmann [194], 2014	32, 64	s.c.	Acute; once daily for 4 days	Y	N	N
	D-cycloserine	Wu [197], 2017	10 mg/side	c.i.	Acute	Y	Y	N
	Melatonin	Tian [183], 2014	1, 5	p.o.	Once daily over 28 days	Y	N	N
	Minocycline	Kumar [153], 2016	25, 50	p.o.	Once daily over 30 days	Y	N	Y
	mS-11	Kawase [142], 2018	10, 30	i.p.	Once daily for 2 weeks	Y	N	N
	Oxytocin	Dai [116], 2018	1 μg/μL; 3 μg/20 μL	i.n.; s.c.	Acute; 7 daily	Y	Y	N
	Oxytocin	Wang [189], 2018	200 μg/kg	i.n.	Acute	Y	Y	N
	Oxytocin	Matsuo [163], 2017	12 μg/kg	i.n.	Chronic for 2 weeks	Y	N	N
	Oxytocin	Hara [135], 2017	0.05–0.2; 0.1	i.n.	Acute; once daily for 2 weeks	Y	N	N
	Pentyl-4-yn-VPA	Foley [127], 2014	84	i.p.	Once daily over 9 days	Y	N	N
	PF3845	Kerr [41], 2016	10	i.p.	Acute	Y	N	Y
	Rapamycin	Zhang [203], 2017	4	s.p.	Once daily over 12 days	Y	Y	N
	SAHA	Foley [127], 2014	5	i.p.	Once daily over 18 days	Y	N	N
	Semax	Malyshev [64], 2013	0.05	i.n.	Once daily over 14 days	Y	N	N
	URB597	Melancia [39], 2018	0.05	i.p.	Acute	Y	Y	N
Psychostimulants and catecholamines	Methylphenidate	Choi [111], 2014	5	i.p.	Acute	N	N	N
	Methylphenidate	Hara [134], 2016	3	i.p.	Acute; once daily over 2 weeks	Y	N	N

Each treatment is shown alongside its study, medication class, dosage volume used (in mg/kg, unless otherwise stated for individual drugs), mode of dosage administration used, dosage timing used, whether the drug tested was effective in alleviating VPA-induced ASD-related impairments (Y/N = Yes/No, where No can also be because that behaviour was not tested in that study), and the results obtained from the experiment in the treated rodents (where they are different from the results in the corresponding VPA rodents). i.p., intraperitoneal injection; s.c., subcutaneous injection; p.o., oral ingestion; i.n., intranasal administration; c.i., cerebral injection; i.c., intracardiac injection; s.p., stomach perfusion; i.g., intragastric administration.

sniffing, latency to sniff, time spent in social zones, latency in social zones, social grooming, aggressive grooming, crossovers to/away from conspecific, flank exploration, and hiding inside a tube (Tables 1, 3). Moreover, many studies that reported measuring several behaviours did not find differences for each measured behaviour, and it is unknown whether the studies that did not report a specific behaviour did so because of a failure to find a significant effect of VPA on that behaviour. Thus, while there is considerable consistency across the studies in reporting some behavioural alteration consistent with an ASD phenotype, the robustness of these changes can be improved in future studies by reporting a minimum standard set of behaviours/measures.

Sex Differences

A current topic of considerable interest in the ASD literature is the difference in incidence and expression of ASD between males and females. In studies where both female and male test subjects were employed, VPA-exposed males showed more robust social impairments than VPA females, suggesting a potential protective/compensatory effect towards social impairment induction in females [55]. In addition, VPA-exposed females (compared to VPA-exposed males) were more likely to exhibit stereotypies occurring earlier in the open field testing session [56, 57] elicit shorter distress-call durations in the ultrasonic vocalisation test [31, 58], and commit more T-maze errors in the T/Y-maze test for cognitive rigidity [53]. In contrast, VPA-exposed males demonstrated a greater reduction in social preference (in the social preference test), social novelty preference (in the social novelty preference test), more stereotypies, more play-fighting in adulthood (in the social interaction test), and delayed T-maze acquisition-phase performance (in trained versions). Given that research in humans suggests ASD may present differently in males and females, we recommend more studies use both male and female samples [59, 60]. At this point, it is unclear whether the VPA rodent model skews the male propensity to have ASD impairments, compared to the normal human population.

Although social interaction decreased in males, VPA-exposed female rodents interestingly spent more time in social interaction [61]. In other studies, VPA-exposed males vocalised less than VPA-exposed females socially [31, 39, 40, 62–65]. Other environmental ASD models (maternal immune activation and prenatal zinc deficiency) in rodents do not always show this sex bias in social impairment [55]. It is unclear, at this stage (owing also to the small animal numbers in published studies), if the VPA model could be more suitable to study these behaviours in detail.

Age Differences

The age at which offspring were tested resulted in a number of relevant outcomes, likely specific to VPA exposure. Interestingly, older ages in the VPA groups had decreased social [66] and total [67] exploration than younger VPA-exposed rodents. Older VPA-exposed rodents had a lower discrimination index in the novel object recognition test compared to younger VPA rodents [68]. This difference in discrimination could have played a role in older VPA rodents' social novelty preference impairment. These results suggest that VPA studies using adolescent rodents may be optimal, as there appear to be larger differences between VPA rodents and controls in these behavioural tests at this age.

Social and Non-Social Novelty

VPA-exposed rodents were also observed to have a decreased preference for novelty. In general, it was found that this preference for familiarity may not be dependent on social context, with VPA-exposed rodents displaying a preference for familiarity in both social and object domains. Indeed, the findings of the reviewed studies in rodents align with behaviours observed in children with ASD, who are often found to be more comfortable with familiar objects as well as people [53]. Given that this preference for familiarity was observed both in social and non-social tests, this may point to both social novelty preference and novel object recognition tests as an indicator of cognitive rigidity (see later) as opposed to social impairment. Alternatively, positive results in both tests may point to memory impairment. Recent studies on the VPA model [69–71], as well as models of rodent autism based on gene knockout [72], seem to support this latter hypothesis.

Effectiveness of Novel Pharmacotherapies in the VPA Model and Suggestions for Future Drug Studies

A wide array of compounds was assessed, and these were found to alleviate some aspects of ASD-relevant behaviour, with few exceptions. Predominantly, social behaviours were evaluated, but a few acted on cognitive rigidity and stereotypies; these did not seem to be restricted to any class of drugs (Table 4).

We had mentioned that a good animal model of ASD should have construct, face, and predictive validity. After reviewing these papers, we can now confirm that the rodent VPA model has these validities. We propose future

studies evaluating novel drugs in the VPA model of ASD, incorporating a few suggestions. We suggest studies include at least one measure from each of the 3 core domains reported here. We also suggest, despite not being yet common in the pre-clinical literature, pre-registration of studies that can avoid (and assess) the extent of publication bias. Importantly, pre-registering studies would further separate pre-diction and post-diction analyses to better delineate the relationship between hypothesis and results, and to better compare different results [73, 74]. As noticed in the therapeutic studies (Table 4), a publication bias appears to exist, whereby only successful treatments have generally been published, whereas unsuccessful treatment trials have not been reported (with the exception of haloperidol [75]).

We further suggest that multiple testing is certainly warranted when results are uncertain, to increase statistical power as well as reproducibility. One study found a transgenerational effect of VPA increasing compulsive/repetitive behaviour in the 1st and 3rd generations of offspring, but not the 2nd [76]. The mechanism for how the behavioural alteration may skip a generation is not discussed in that paper, and such a result would need robust replication. In addition, we suggest that many of the one-off pilot studies of potential treatments should be replicated, to verify their efficacy in the VPA rodent model and as subsequent candidates for human ASD trials. This result suggests possible publication bias for which we make some suggestions to address for future studies.

In terms of novel drugs to be trialled for this purpose, we suggest anxiolytic medications such as 3,4-methylenedioxymethamphetamine (MDMA) which has been successfully used to treat social anxiety in autistic adults [77]. From Table 4, it appears that especially Korean Red ginseng [10] and donepezil [78] appear to alleviate all 3 core ASD behaviours studied here, from different drug classes. Most of the trials explored primarily social behaviours, but it is worth bearing in mind that the other 2 behaviours should not be excluded, especially as different ASD patients have different degrees of impairment in each of these domains.

Suggestions for Future VPA-Model-Specific Research

It was surprising to see none of the 150 papers reviewed here used cross-fostering of animals. Cross-fostering addresses the potential confounding factor of whether or not the VPA-challenge influences maternal behaviour and environment [79]. Thus, we suggest future studies apply cross-fostering to determine whether the influence of maternal treatment with VPA may be a significant confounder. Other limitations of the VPA model include that the VPA injection is not 100% effective and can lead to malformations or pregnancy loss [80].

We also suggest investigating more complex and insightful features of human ASD in the VPA model. Rodent behavioural equivalents have been developed for a number of superior neural functions affected in ASD, including: visual emotion recognition [81, 82]; decision-making under uncertainty (e.g., reversal learning and the Iowa gambling test) [83, 84]; various aspects of empathic processing [85]; fine motor coordination [86–88]; and sensory temporal-binding windows [86, 89, 90]. These are common impairments in humans with ASD [91–96]. This would complement the studies assessing the core behavioural impairments in ASD, to give us a more wholesome understanding of ASD in general.

Limitations

Only English-language papers were reviewed, and only 6 databases were screened, possibly resulting in articles inadvertently being excluded. In addition, this review addresses only the VPA-induced rodent model of ASD, and other species and other induced causes of ASD may not yield the same results, such that extrapolations across causative models and different animal species should be made with caution.

Conclusion

This is the first systematic literature review providing evidence and cataloguing of different VPA-induced autism behaviours as well as potential treatments explored up to date. Unlike previous reviews on this topic, this review allows investigators to track where VPA causative and ASD treatment pre-clinical models have succeeded and failed, in different aspects of the ASD phenotype. Future directions include exploring a variety of different drug treatments to compare against this list of previous trials using the VPA rodent model of autism, to expedite the discovery of direct and effective drug treatments for the different needs of different patients afflicted with ASD-related malfunctioning behaviours. It can also include improving the current animal model of ASD to exponentiate this progress in finding novel drug treatments.

The use of 400–600 mg/kg VPA, administered i.p. or s.c. to the mother around GD 12.5, induces behaviours resembling all 3 core impairments defining ASD in the offspring when tested postnatally: social impairments, cognitive rigidity, and repetitive behaviours. Ideally, ro-

dents would be in the adolescent age range when behaviourally tested, and more studies should use both male and female rodents to correspond with the fact that ASD in the human population affects both sexes.

The valproic-acid-induced rodent model of autism is well established and likely to remain for the foreseeable future a widely utilised model to test putative efficacy of pharmacological agents on behavioural and social elements in the autistic spectrum. However, the VPA model is relatively homogenous in aetiology and phenotype, limiting generalisability, and important species differences exist. For example, rodents are generally more resistant to the effects of pharmacological agents. With the continual evolution of defining autism phenotypes and new opportunities for pharmacological and non-pharmacological intervention, the rodent VPA model of autism may become more specific, or potentially redundant. In addition, robust models of autism such as VPA induction provide safe, if not obligatory, opportunities to consider synergistic therapeutic opportunities as well as potential adverse effects.

The individual causes of autism remain largely unknown, and it is a reasonable proposition that most patients would not have had birth mothers taking VPA during pregnancy, raising questions as to the validity of the VPA model to human autism. Nonetheless, evidence of intervention efficacy in the VPA model provides insight into potential clinical opportunities, as it is well established that VPA is a striking risk factor for ASD, therefore an important strategy for studying ASD development and triggers, especially for novel therapeutics. It also does not exclude that other molecular mechanisms may play a part in ASD pathophysiology, from other environmental risk factors, as is evident in other animal models of autism in the literature.

In 5/10 years' time, we expect VPA rodent models of autism to have generated more clinical drug candidates to treat the 3 behavioural diagnostic criteria for autism. In addition, autism diagnostic criteria may be updated, especially distinct for girls versus boys. Following the success of VPA using the behavioural testing repertoire above, other causative agents could be studied to investigate new treatment drugs for autism.

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