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RESEARCH REPORT

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The Arctic/Swedish APP mutation alters the impact of chronic stress on cognition in mice

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Abstract

Chronic stress is a major risk factor for developing Alzheimer's disease (AD) and promotes the processing of amyloid precursor protein (APP) to β-amyloid (Aβ). However, the precise relationship of stress and disease-typical cognitive decline is presently not well understood. The aim of this study was to investigate how early life stress may affect cognition in adult mice with and without soluble Aβ pathology typical for the early stages of the disease. We focussed on sustained attention and response control, aspects of cognition mediated by the prefrontal cortex that are consistently impaired both in early AD and after chronic stress exposure. Young wild-type mice as well as transgenic arcAβ mice overexpressing the *hAPParc/swe* transgene were exposed to a chronic unpredictable stress paradigm (age 3–8 weeks). At 15 weeks, these mice were tested on the 5-choice serial reaction time task, a test of sustained attention and executive control. We found that, expectedly, chronic stress increased impulsive choices and impaired sustained attention in wild-type mice. However, the same treatment reduced impulsivity and did not interfere with sustained attention in arcAβ mice. These findings suggest an unexpected interaction between chronic stress and Aβ whereby Aβ-pathology caused by the *hAPParc/swe* mutation prevented and/or reversed stress-induced cognitive changes through mechanisms that deserve further investigation. They also indicate that Aβ, in modest amounts, may have a beneficial role for cognitive stability, for example by protecting neural networks from the impact of further physiological or behavioural stress.

KEYWORDS

Alzheimer's disease, APP, impulsivity, stress, sustained attention

Abbreviations: 5-CSRTT, 5-choice serial reaction time task; AD, Alzheimer's disease; APP, amyloid precursor protein; Aβ, β-amyloid; CORT, corticosterone; PFC, prefrontal cortex; RM, repeated measures; STR, unpredictable chronic stress; Wt, wild type.

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1 | INTRODUCTION

Although the predominant behavioural symptoms of Alzheimer's disease (AD) are severe memory deficits, compromised attention and executive function are also prominent even at early stages of the disease and most likely reflect prefrontal cortex (PFC) dysfunction (Arnsten, 2015; Baddeley, Baddeley, Bucks, & Wilcock, 2001; Bentley, Driver, & Dolan, 2008; Perry & Hodges, 1999; Romberg, Mattson, Mughal, Bussey, & Saksida, 2011; Sahakian, Jones, Levy, Gray, & Warburton, 1989). The PFC is also one of the brain regions consistently affected by β-amyloid (Aβ) plaque pathology in AD patients, although the presence of plaques does not predict cognitive decline. Instead, neural network dysfunction and cognitive deficits in the early stages of AD more readily correlate with elevated soluble intracellular Aβ-oligomers and synaptic degeneration (Billings, Oddo, Green, McGaugh, & LaFerla, 2005; Braak & Braak, 1991; Knobloch, Konietzko, Krebs, & Nitsch, 2007; LaFerla, Green, & Oddo, 2007; Palop & Mucke, 2010; Selkoe, 2002).

The cause of AD is most likely multi-factorial, but chronic stress is not only associated with a higher incidence of sporadic AD (Johansson et al., 2013; Pardon, 2011; Reitz, Brayne, & Mayeux, 2011), but also with persistent changes to the functional and structural integrity of the PFC. Moreover, chronic stress promotes the post-translational processing of amyloid precursor protein (APP) to Aβ in the cortex (Baglietto-Vargas et al., 2015; Catania et al., 2009; Dong et al., 2012; Jeong et al., 2006), and acute stressors increase interstitial fluid Aβ in humans (Kang, Cirrito, Dong, Csernansky, & Holtzman, 2007). However, the interaction of stress, (soluble) amyloid pathology and cognitive decline is only poorly understood. Therefore, we aimed to investigate how early life stress may affect cognition in adult mice with and without Aβ oligomer pathology typical for the early stages of the disease. We focussed on two aspects of cognition mediated by the PFC: sustained attention and impulsivity.

To model abundant cerebral Aβ oligomer pathology characteristic for early AD, we used mutant arcAβ mice that overexpress human APP 695 with the Arctic and Swedish mutation (*hAPP*$_{arc/swe}$, Knobloch et al., 2007). ArcAβ and age-matched wild-type (wt) littermates were exposed to an unpredictable chronic stress (STR) paradigm between the ages of 3 and 8 weeks, that is when Aβ oligomers begin to accumulate in ArcAβ mice (Figure 1, Knobloch et al., 2007; Lord et al., 2009). In the light of data showing that both stress and Aβ cause robust structural and functional changes in the PFC, and that both stress and AD are associated with changes in sustained attention (Romberg, Bussey, & Saksida, 2012a; Sahakian & Coull, 1993), we subsequently tested these animals on the 5-choice serial reaction time task (5-CSRTT), an established test of visuo-spatial attention and response control that has proven powerful in assessing multiple aspects of PFC function in rodents and humans (Robbins, 2002; Romberg, Horner, Bussey, & Saksida, 2012b; Romberg et al., 2011; Worbe, Savulich, Voon, Fernandez-Egea, & Robbins, 2014).

2 | MATERIALS AND METHODS

2.1 | Animals

Male hemizygous founder arcAβ mice on a C57/BL6 background (Knobloch et al., 2007; Nilsberth et al., 2001) were kindly provided by Roger Nitsch (University of Zurich, Switzerland). Age-matched, arcAβ and wt mice used in experiments were generated from founder arcAβ matings with wt female C57BL/6 mice. Only male mice were used for this study.

Mice were housed in groups of 2–4 animals, with ad libitum food and water under standard laboratory conditions (light–dark cycle: 12:12 hr, lights on at 7 a.m.; temperature: 22 ± 1°C; relative humidity: 55 ± 5%). Animal breeding and experimental procedures were conducted in compliance with Directive 2010/63/EU of the European Commission and approved by the local animal ethics

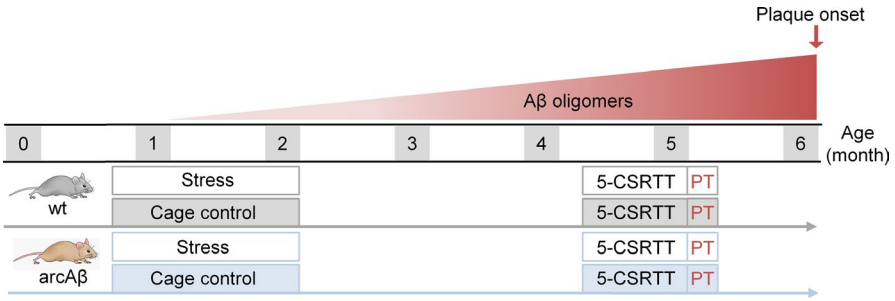

FIGURE 1 Timeline of experimental procedures. Test cohorts of wt (light grey) and arcAβ mice (light brown) were either exposed to a chronic unpredictable stress paradigm (stress, STR), or handled daily in their home cages (Cage Control) between the ages of 3 and 8 weeks. When 17 weeks old, animals were trained on the 5-CSRTT until their performance was stable. Animals were then challenged on probe trials (PT) with shorter stimulus durations. The evolution of β-amyloid pathology in arcAβ mice (see Knobloch et al., 2007) is shown above the timescale. [Colour figure can be viewed at wileyonlinelibrary.com]

council of the Government of Upper Bavaria, Germany (Gz. 170-2).

2.2 | Chronic unpredictable stress paradigm (STR)

Groups of age-matched, male wt ($n = 22$) and arcAβ mice ($n = 21$) were exposed to an established STR paradigm between postnatal week 3–8 (Dias-Ferreira et al., 2009). In brief, six low-intensity stressors were applied in a pseudo-random fashion: (a) shaking in a confined space (plastic box, 10 × 10 × 5 cm, with six breathing holes in lid) on an orbital agitator (100 rpm), for 1 hr; (b) immobilization in a 50-ml Falcon™ tube (holes on both sides), for 30 min; (c) restraint in a plastic box (see above) paired with white noise exposure, for 1 hr; (d) damp bedding in home cage (200 ml of water per cage), for 12 hr; (e) tilted cage (45° tilt) for 12 hr; and (f) overnight illumination: lights on for 24 hr. Procedures (a)–(c) were only carried out during the light phase of the light–dark cycle, whereas procedures (d)–(f) were only performed during the dark phase. The weekly schedule of pseudo-randomized procedures was repeated four times over four consecutive weeks (total 28 days of STR exposure). Littermate control mice (wt: $n = 41$, arcAβ: $n = 28$) remained in their home cages and were handled twice daily for 5 min at times yoked to the STR schedule.

2.3 | Corticosterone response to an acute stressor

In order to compare the endocrine responses of arcAβ and wt mice to an acute stressor, a separate cohort of 2-month-old mice ($n = 10$ for each genotype) were acutely restrained (immobilization in a 50-ml Falcon™ tube for 10 min between 07:30 and 08:30) after which a blood sample (tail venipuncture) was obtained and subsequently assayed for corticosterone (CORT), using a sensitive radioimmunoassay (MP Biochemicals).

2.4 | Behavioural procedures

2.4.1 | Apparatus

Behavioural testing was conducted in a touch screen-based automated operant system for mice (Campden Instruments Ltd.) and the associated software for task delivery, data acquisition, storage and analysis (AbetII, Lafayette Instruments; Horner et al., 2013; Mar et al., 2013). The trapezoid chambers of the apparatus were composed of three black plastic walls opening on to the touch screen. On the wall opposite, the touch screen was a reward magazine unit with light and infrared beams to detect entries, for delivery of a liquid reward (diluted condensed milk 1:5, 0.2 ml per correct choice).

2.4.2 | Touch screen pre-training

For behavioural testing, mice were exposed to a standard food restriction paradigm to maintain a body weight of 85%–95% of pre-restriction weight. Water was available ad libitum. After reaching a stable body weight, animals were "shaped" in the touch screen test apparatus, as previously described (Mar et al., 2013; Romberg et al., 2011, 2012b). Briefly, the first stage of shaping involved habituation to the operant chamber (30 min/day, until mice readily consumed the milk reward on two consecutive days).

Next, mice had to learn to associate a stimulus on the screen with a milk reward in the magazine. A white square appeared in one of five response windows on the screen. After 30 s, the stimulus disappeared, coinciding with a tone, the onset of the magazine light and the delivery of a milk reward. When the animal collected the reward, the magazine light extinguished and the next trial commenced with the display of a new stimulus. The criterion for moving onto the next stage was 30 completed trials within 1 hr, on 2 consecutive days.

During the third stage of shaping, animals were required to learn to touch the stimulus to receive the milk reward; the stimulus remained on the screen until the mouse touched the stimulus. Collection of the reward triggered a 5 s inter-trial interval (chamber light-on, no stimulus, magazine inactive) after which the next trial commenced. Training continued until the animal completed 30 trials within 15 min for two consecutive days in a row.

The final stage of shaping introduced the "initiation" procedure. At the onset of each trial, the magazine was illuminated, and the animal was required to initiate stimulus delivery by poking its nose into the reward magazine. Once animals readily initiated trials and completed 30 trials within 20 min for 2 consecutive days, they entered the training phase of the 5-CSRTT. The entire pre-training procedure lasted approximately 2 weeks.

2.4.3 | 5-choice serial reaction time task

Training phase

Mice were 15 weeks old when task training started, at which stage they are known to show elevated Aβ oligomer levels, but no plaque pathology, in the cortex and hippocampus (Knobloch et al., 2007). The general 5-CSRTT task procedure has been described previously (Mar et al., 2013; Romberg et al., 2012b). Mice were trained to respond to brief flashes of light pseudo-randomly displayed in one of the five spatial locations on the touch screen. Mice were

tested 5–6 days a week, 60 trials a day (or up to 1 hr). In contrast to the last stage of pre-training, a nose poke to the magazine did not result in the immediate display of a stimulus. Instead, the stimulus was delivered after a 5 s delay (the delay period), during which the animal was required to attend to the screen. If an animal prematurely touched the screen during this delay, the response was recorded as premature and followed by a 5 s time out interval (house light-off, magazine inactive). The stimulus duration was initially set to 6 s, followed by a limited holding period of 5 s, during which the stimulus was absent but the animal was still able to respond to the location. Responses during stimulus presence or limited holding period were recorded either as correct (response to the stimulus window) or incorrect (response to any other window). A correct choice was rewarded, an incorrect response triggered a 5 s time out, followed by the 5 s inter-trial interval. Failure to respond to any window either during stimulus display or limited holding period was recorded as an omission and followed by a 5 s time out and a 5 s inter-trial interval. Additional, perseverative responses to the screen after premature (during time out), correct (before collecting the reward) and incorrect (during time out) choices were recorded. However, such responses were very rare and therefore not further analysed. Once the performance of a mouse stabilized at 6 s stimulus duration (>80% accuracy, <20% omissions on 3 out of 4 consecutive days), the stimulus duration was reduced to 4 s and consecutively to 3, 2 and 1.5 s, whenever criterion was reached at the given stimulus duration.

Baseline performance

After reaching criterion with the 1.5 s stimulus, animals were tested for 2 more days. The mean measures of those 2 days were used to analyse baseline performance.

Probe trials

After completing training at 1.5 s stimulus duration, animals were exposed to four consecutive probe sessions. To increase attentional demand, these sessions consisted of 60 trials with reduced stimulus durations (1.5, 1.3, 1.1, 0.9 and 0.7 and 0.5 s). Within each session, each stimulus duration was presented 10 times. The sequence of stimulus durations within a session was determined pseudo-randomly, with a single stimulus duration never presented more than twice (2 trials) in a row.

2.5 | Data analysis

Attention and response control were assessed by measuring response accuracy (correct trials divided by correct plus incorrect trials in %, excluding omitted trials), omissions (omitted divided by total trials), premature responses (premature trials divided by total), perseverative responses (per choice), and response and magazine latencies to/after correct choices. All data are shown as means ± *SEM*. Data were submitted to one-way or repeated measures (RM) ANOVA, as appropriate. Simple main effects were subsequently analysed for within-subject effects using Sidak's multiple comparison post hoc test. All statistical analyses were performed at a significance level of $\alpha = 0.05$, using SPSS (version 17) software.

3 | RESULTS

Both wt and arcAβ mice with/out STR acquired the general 5-CSRTT procedure at similar rates and required a similar number of sessions to reach the criterion of stable baseline performance (>80% correct, <20% omissions at 1.5 s stimulus duration for 3 of 4 consecutive days; mean sessions to criterion wt: 20.4 ± 0.9; arcAβ: 19.7 ± 0.7;

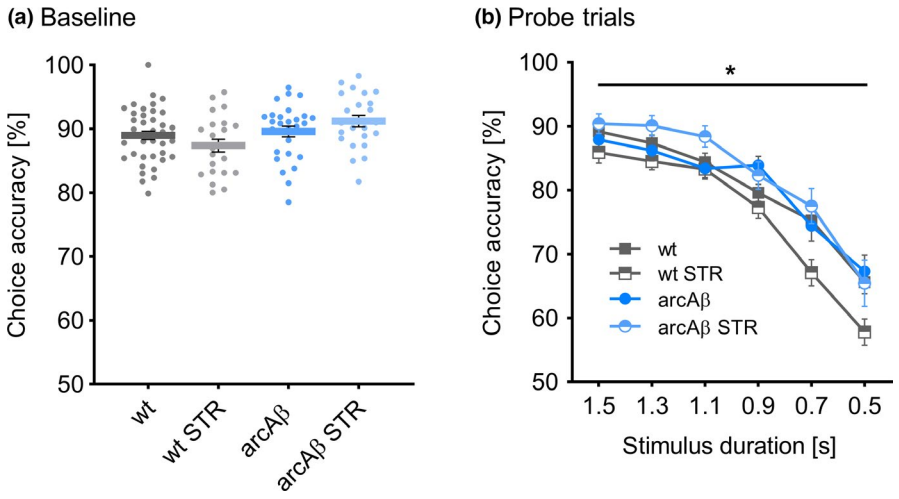

FIGURE 2 Sustained attention is reduced in adult wt, but not arcAβ, mice exposed to STR. Mean response accuracies during (a) baseline performance and (b) probe trials with variable stimulus duration are shown. Data are presented as mean ± *SEM*. *Simple main effect of genotype on STR mice, $p < 0.05$. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 RM ANOVA results for probe trial choice accuracies, with genotype and STR as between-subjects factors, and stimulus duration as the within-subject factor

Main effects		Interactions		Post hoc simple main effects	
STR	$F_{1,108} = 0.86$, $p = 0.355$	**STR × genotype**	**$F_{1,108} = 9.1, p = 0.003$**	**STR on wt**	**$F_{1,108} = 8.58, p = 0.004$**
				STR on arcAß	$F_{1,108} = 2.0, p = 0.158$
		STR × stimulus duration	**$F_{5,540} = 2.5, p = 0.013$**		
		STR × genotype × stimulus duration	$F_{5,540} = 1.2, p = 0.295$		
Genotype	**$F_{1,108} = 10.7$, $p = 0.001$**	**Genotype × STR**	**$F_{1,108} = 9.1, p = 0.003$** (same as above)	Genotype on no-STR mice	$F_{1,108} = 0.04, p = 0.844$
				Genotype on STR mice	**$F_{1,108} = 16.3, p < 0.001$**
		Genotype × stimulus duration	$F_{5,540} = 0.8, p = 0.550$		
Stimulus duration	**$F_{5,540} = 133.1$, $p < 0.0001$**				

Significant effects are shown in bold.

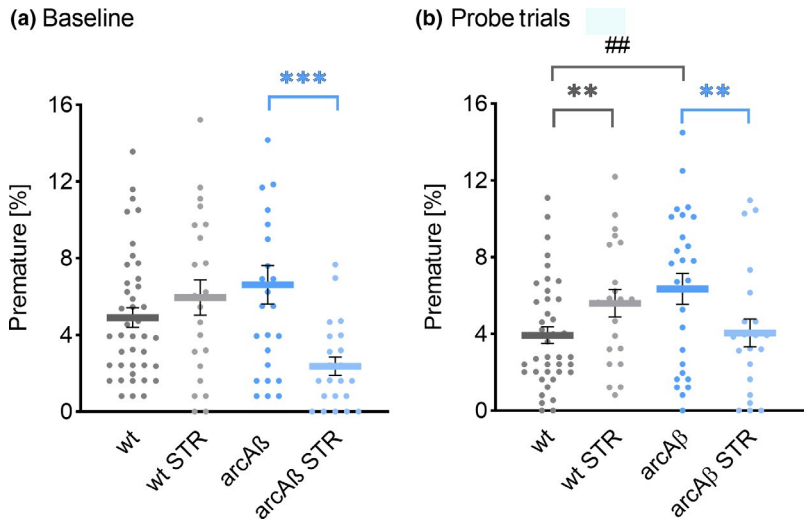

FIGURE 3 5-CSRTT premature responses during (a) baseline performance, ***simple main effect of STR, $p < 0.001$, and (b) probe trials with variable stimulus duration, **simple main effect of STR, $p < 0.01$, ##simple main effect of genotype, $p < 0.01$. Data are presented as mean ± *SEM*. [Colour figure can be viewed at wileyonlinelibrary.com]

STR-wt: 20.0 ± 0.9; STR-arcAβ: 20.9 ± 0.9; one-way ANOVA with genotype and STR as between-subjects factors: $F_{3,108} = 0.31$, $p = 0.8$).

3.1 | STR impairs sustained attention in wt, but not arcAβ, mice

Choice accuracy on the 5-CSRTT reflects the ability to sustain attention over an extended period of time. Although 5-CSRTT choice accuracies of STR-wt mice were similar to those of unstressed wt mice at baseline (Figure 2a, one-way ANOVA with genotype and STR as between-subjects factors: $F_{3,108} = 2.1$, $p = 0.09$, no main effect of STR: $p = 0.69$, or STR × genotype interaction, $p = 0.18$), they were significantly reduced on the probe trials with shorter stimulus durations (Figure 2b, RM ANOVA, Table 1). Thus, STR exposure caused long-lasting sustained attention deficits in wt mice.

In contrast, arcAβ mice did not display sustained attention deficits either at baseline (Figure 2a, one-way ANOVA with genotype and STR as between-subjects factors $F_{3,108} = 2.1$, $p = 0.09$; no main effect of genotype: $p = 0.07$) or on the probe trials (Figure 2b, Table 1). Surprisingly, unlike in wt mice, STR had no effect on choice accuracies in arcAβ mice even when animals were challenged with shorter stimulus durations on the probe trials (Figure 2b,

TABLE 2 ANOVA results for premature responses

Main effects		Interactions		Post hoc simple main effects	
a. Baseline: one-way ANOVA of premature responses with genotype and STR as between-subjects factors					
STR	**$F_{1,108} = 2.8, p = 0.096$**	**STR × genotype**	**$F_{1,108} = 8.3, p = 0.005$**	STR on wt	$F = 0.77, p = 0.382$
				STR on *ArcAβ*	**$F_{1,108} = 9.8, p < 0.005$**
Genotype	$F = 0.3, p = 0.570$			Genotype on no-STR mice	$F_{1,108} = 3.3, p = 0.072$
				Genotype on STR mice	**$F_{1,108} = 4.9, p = 0.027$**
Overall	**$F_{3,108} = 3.5, p = 0.017$**				
b. Probe Trials: one-way ANOVA of premature responses with genotype and STR as between-subjects factors					
STR	$F_{1,108} < 0.01, p = 0.990$	**STR × genotype**	**$F_{1,108} = 9.3, p = 0.003$**	**STR on wt**	**$F_{1,108} = 5.2, p = 0.025$**
				STR on ArcAβ	**$F_{1,108} = 4.2, p = 0.043$**
Genotype	$F_{1,108} = 0.03, p = 0.865$			**Genotype on no-STR mice**	**$F_{1,108} = 6.5, p = 0.012$**
				Genotype on STR mice	$F_{1,108} = 3.4, p = 0.066$
Overall	$F_{3,108} = 2.9, p = 0.021$				

Significant effects are shown in bold.

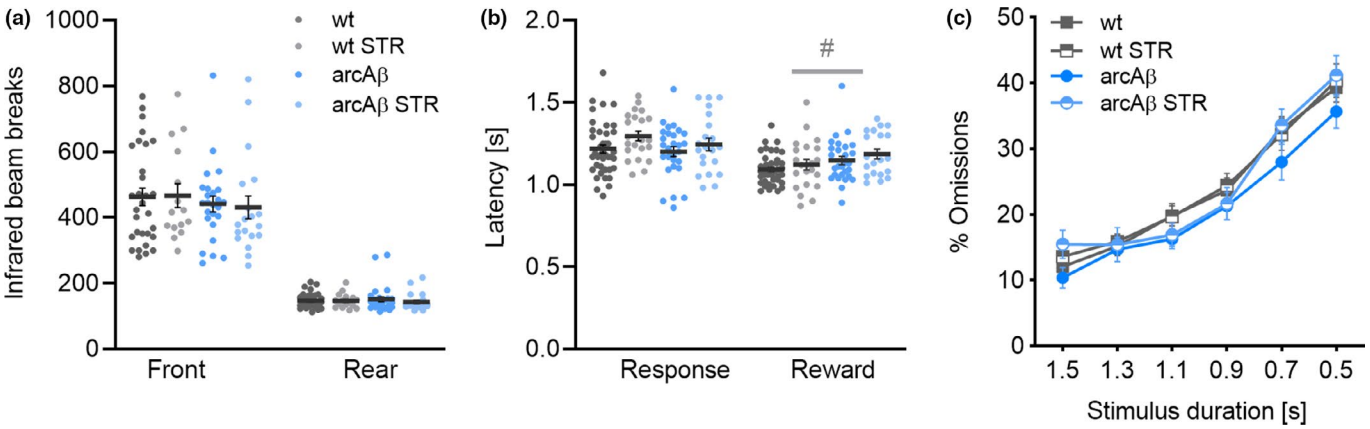

FIGURE 4 Control measures of general task performance on the 5-CSRTT. (a) Mean number of infrared beam breaks. (b) Mean percentage of omitted trials. (c) Mean latency of response and reward collection. Data are presented as mean ± *SEM*. *Simple main effect of STR on wt mice, $p < 0.05$; #main effect of genotype, $p < 0.05$. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1). Thus, the interaction between STR and the *hAPP*$_{swe/arc}$ genotype resulted in an unexpected phenotype where the arcAβ genotype seemingly neutralized the impact of previously experienced STR.

3.2 | Stress oppositely influences impulsivity in wt and arcAβ mice

Premature responses on the 5-CSRTT (screen touches after trial initiation but before stimulus onset) provide a surrogate measure of impulsivity, a cognitive trait modulated by complex interactions between PFC structures and the ventral striatum (Dalley & Robbins, 2017; Mar et al., 2013; Robbins, 2002). Similar to choice accuracy, premature responding of wt mice was altered by previous exposure to STR: STR-wt and wt mice initially made a similar number of premature errors at baseline (Figure 3a, RM ANOVA, Table 2a), but STR-wt mice made significantly more premature responses than unstressed wt mice on the probe trials (Figure 3b, RM ANOVA, Table 2b). Thus,

TABLE 3 Statistical test results of 5-CSRTT control measures on the probe trials

Measure	Test	Main effects
Infrared beam entries	One-way ANOVA	Overall: $F_{3,108} = 0.8$, $p = 0.127$ Genotype: $F_{1,108} = 0.9$, $p = 0.928$ STR: $F_{1,108} = 0.4$, $p = 0.516$ Genotype x STR: $F_{1,108} = 0.3$, $p = 0.572$
Omissions	RM ANOVA	**Stimulus duration: $F_{5,550} = 163$, $p < 0.0001$** Genotype: $F_{1,108} = 1$, $p = 0.320$ STR: $F_{1,108} = 1.3$, $p = 0.263$ Genotype × STR: $F_{1,108} = 0.6$, $p = 0.431$
Response latency	One-way	Overall: $F_{3,108} = 1.5$, $p = 0.180$ Genotype: $F_{1,108} = 1.1$, $p = 0.296$ STR: $F_{1,108} = 3.1$, $p = 0.054$ Genotype × STR: $F_{1,108} = 0.3$, $p = 0.571$
Reward collection latency	One-way	Overall: $F_{3,108} = 2.8$, $p = 0.043$ **Genotype: $F_{1,108} = 5.6$, $p = 0.017$** STR: $F_{1,108} = 1$, $p = 0.164$ Genotype × STR: $F_{1,108} = 0.4$, $p = 0.852$

Significant effects are shown in bold.

previous STR exposure persistently increased impulsive action in wt mice.

Moreover, premature responding was also affected by the *hAPP*$_{arc/swe}$ genotype: although initially performing similar to wt mice at baseline (Figure 3a, Table 2a), arcAβ mice made *more* premature responses than wt mice when challenged on the probe trials (Figure 3b, RM ANOVA, Table 2b). Thus, both STR and Aβ oligomer pathology increased impulsivity.

However, when arcAβ mice were exposed to STR, the effect on impulsivity was the opposite to that in wild-type mice: whereas STR *increased* probe trial premature responding in wt mice, as stated above, STR significantly *decreased* premature responding in arcAβ mice both at baseline and on probe trials (Figure 3a,b, Table 2a,b).

In summary, these data show that while early life STR and familial APP mutations independently generate more impulsive adult phenotypes, their effects are counteractive rather than additive.

3.3 | 5-CSRTT results were not influenced by major procedural deficits

Wild-type and arcAβ mice showed no major differences on measures of general task performance that might have indicated gross motivational or motoric abnormalities (Figure 4). Probe trial activity levels (front and rear infrared beam breaks, Figure 4a), response latencies (Figure 4b) and omissions (Figure 4c) were similar in both genotypes (Table 3). However, there was a tendency for slightly longer reward collection latencies in arcAβ mice (Figure 4b, Table 3). STR had no significant effect on any of the control measures (Figure 4a–c, Table 3).

3.4 | Similar endocrine profiles in wt and arcAβ mice

Alterations of hypothalamo–pituitary–adrenal (HPA) function have been reported in various transgenic models of AD (Dong et al., 2008; Green, Billings, Roozendaal, McGaugh, & LaFerla, 2006; Lee, Martin, Maple, Tharp, & Pratley, 2009; Touma et al., 2004), but such information is not available for the arcAβ line. We therefore tested in a comparable paradigm, how serum corticosterone (CORT) of arcAβ mice responded to acute stress (10 min restraint), one of six semi-randomly applied stressors used in the chronic STR paradigm. We found that basal and acute stress-induced serum CORT levels did not differ significantly in arcAβ ($n = 10$) and wt mice ($n = 10$; Figure 5; basal CORT: wt 6.6 ± 1.1 vs. arcAβ 7.0 ± 1.3 ng/ml; stress-induced CORT: wt 124.7 ± 7.35 vs. arcAβ 119.1 ± 7.6 ng/ml). A RM ANOVA with genotype as between-subjects factor and acute stress as within-subject factor returned a main effect of acute stress ($F_{1,19} = 13.1$, $p < 0.001$) and no effect of genotype or interaction (all $F < 1$, $p > 0.5$). The similar endocrine profiles of wt and arcAβ mice suggest that the differential cognitive effects of STR in wt and arcAβ mice cannot be ascribed to genotype-dependent alterations in endocrine function.

4 | DISCUSSION

4.1 | Summary

We aimed to address how a high cerebral Aβ oligomer load and exposure to chronic stress affect sustained attention and executive control, and how these two factors may interact. We found that early life STR exposure alone caused an impairment of sustained attention and a more impulsive phenotype in adult mice. In contrast, a high cerebral Aβ oligomer load, that is the arcAβ genotype alone, had no impact on adult sustained attention, but also increased adult impulsivity. When both factors were combined, a very different picture emerged: STR *decreased*, rather than *increased,* impulsivity in the arcAβ mouse model of familial AD. Moreover, the arcAβ genotype prevented the

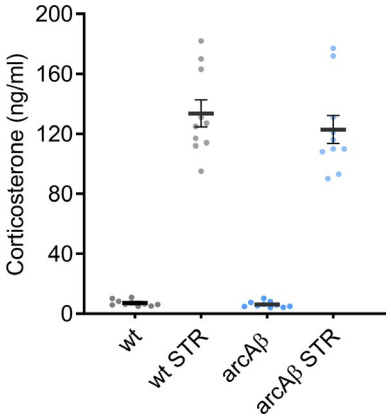

FIGURE 5 Hypothalamo–pituitary–adrenal function is similar in wt and arcAβ mice. Serum corticosterone (CORT) levels were assessed under basal conditions and after exposure of mice to an acute stressor (10 min restraint). ***Main effect of acute stress, $p < 0.001$. Data are presented as mean ± *SEM*. [Colour figure can be viewed at wileyonlinelibrary.com]

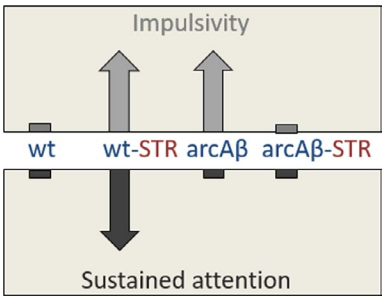

FIGURE 6 Schematic summary of effects of early life stress and *hAPPswe/arc* overexpression on adult impulsivity and sustained attention. STR increased impulsivity in adult wt mice, but reduced impulsivity in adult arcAβ mice. Furthermore, STR impaired sustained attention in wt mice, but had no effect in adult arcAβ mice. [Colour figure can be viewed at wileyonlinelibrary.com]

detrimental effects of early life STR on adult sustained attention (Figure 6).

4.2 | Stress and Aβ oligomers independently increase impulsive action via distinct, counteracting mechanisms

Our study revealed that both STR and $hAPP_{arc/swe}$ overexpression increase premature responding on the 5-CSRTT, a measure of impulsivity. The rise of premature responses after STR is consistent with previous reports of stress-induced increases in impulsivity in rodents (Baarendse, Counotte, O'Donnell, & Vanderschuren, 2013; Comeau, Winstanley, & Weinberg, 2014) and humans (Bosker, Neuner, & Shah, 2017; Oswald et al., 2007). In contrast, previous 5-CSRTT data from AD mouse models other than arcAβ showed no changes in impulsivity (Romberg et al., 2011, 2012b), suggesting that the increase in premature responses we report here is specific to the $hAPP_{arc/swe}$ mutation and the resulting Aβ oligomer pathology. In AD patients, pathological impulsivity often develops on par with the progression of other cognitive impairments, although it remains unclear whether response inhibition is selectively affected, or is compromised due to more general cognitive slowing and/or episodic memory deficits (Rochat et al., 2008, 2013). The results from arcAβ mice presented here suggest that increased impulsivity may, at least in part, be a direct consequence of the early build-up of Aβ oligomers in the brain.

Further studies are required to investigate the precise mechanisms underlying the increase of impulsivity both after STR and *hAPPswe/arc* overexpression, but because the presence of one factor counteracted the effect of the other, STR and the *hAPPswe/arc* genotype may affect impulsivity via distinct, yet interacting mechanisms. Impulsivity in rodents is tightly regulated by a complex bidirectional fronto-striatal network (Dalley, Mar, Economidou, & Robbins, 2008; Dalley & Robbins, 2017). Specifically, response control is regulated by the balance of dopamine levels in the core and the shell region of the nucleus accumbens (Baarendse et al., 2013; Dalley & Robbins, 2017; Diergaarde et al., 2008), which is modulated by afferents from the PFC (Luchicchi et al., 2016), ventral hippocampus (Abela, Dougherty, Fagen, Hill, & Chudasama, 2013), anterior cingulate cortex and by the ascending monoamine systems (Dalley & Robbins, 2017; Dalley et al., 2008). Notably, nucleus accumbens dopamine is altered both after early life stress (Baarendse et al., 2013; Bosker et al., 2017; Oswald et al., 2007; Watt, Weber, Davies, & Forster, 2017) and in other APP mouse models of familial AD (Perez et al., 2005; Von Linstow et al., 2017), which may explain the more impulsive phenotype we observed in both conditions. Furthermore, the paradox counteracting effects of STR and the *hAPPswe/arc* genotype may be explained by independent changes to distinct striatal afferents. For example, Aβ oligomer pathology may have primarily caused functional changes in the PFC that affect PFC-striatal signalling and dopamine levels, for example in the nucleus accumbens core. STR exposure, on the other hand, may have primarily affected dopamine in the nucleus accumbens shell, for example via permanent changes to the ascending monoaminergic system (Dunn, Swiergiel, & Palamarchouk, 2004; Forster et al., 2006; Watt et al., 2017). Combining both STR and the *hAPPswe/arc* genotype may therefore have caused a relative accumbal core/shell dopamine balance, and an impulsive phenotype, comparable to untreated wild-type mice.

However, there are other potential explanations for the differential effects of STR in both genotypes. For example, STR may have reduced the levels of Aβ oligomers in the PFC of arcAβ mice, which may explain the observed decline of impulsivity in comparison with unstressed arcAβ

mice. Indeed, a recent study reports that an early life stress paradigm reduced the amount of Aβ in the hippocampus of 4-month-old *APP/PS1* transgenic mice, a different mouse model of AD (Hoeijmakers et al., 2017). Potential mechanisms underlying this include the following: changes in post-translational APP processing, downregulation of APP expression, epigenetic silencing of APP synthesis and/or an increase of Aβ clearance. Notably, however, stress influences post-translational processing of APP (Catania et al., 2009) towards amyloidogenesis, that is Aβ enhancement; the effects of stress likely occur via beta-secretase 1, whose promoter includes a glucocorticoid response element (Lahiri, Ge, & Maloney, 2005). Although epigenetic modulation/silencing of APP expression has, to our knowledge, not been demonstrated so far, we have previously shown that early life stress epigenetically modulates the expression of glucocorticoid receptors and other stress-related neuropeptides in adulthood (Bockmühl et al., 2015; Murgatroyd et al., 2009). Finally, it is also plausible that STR modulates clearance of Aβ, for instance by altering the rate of phagocytosis by microglia (Hoeijmakers, Lesuis, Krugers, Lucassen, & Korosi, 2018).

Yet another explanation for the less impulsive phenotype of STR-arcAβ mice may be found in the potentially neuroprotective effects of corticotropin-release hormone against Aβ toxicity: several in vitro studies report increased synaptic/neuronal survival of Aβ-treated cells in the presence of corticotropin-release hormone, and/or a shift towards non-amyloidogenic APP cleavage (Bayatti, Zschocke, & Behl, 2003; Facci et al., 2003; Lezoualc'h, Engert, Berning, & Behl, 2000).

4.3 | Chronic stress persistently impairs sustained attention in adult wild-type mice

We found that STR, but not *hAPPswe/arc* overexpression, caused persistent sustained attention deficits. The STR-induced deficits are consistent with other reports of impaired attention (and increased impulsivity) after similar stress paradigms in rodents (Baarendse et al., 2013; Comeau et al., 2014; Tzanoulinou, Riccio, de Boer, & Sandi, 2014) and humans (Bosker et al., 2017; Oswald et al., 2007) and may relate to stress-induced anatomical and/or functional changes to the PFC (Arnsten, 2015; Watt et al., 2017). For example, STR persistently alters GABA-ergic signalling in the prelimbic and orbitofrontal cortex (Tzanoulinou et al., 2014), correlating with reduced response accuracies on the 5-CSRTT. Furthermore, the serotonergic and adrenergic systems are highly responsive to stress-associated neuroendocrine activity (Dunn et al., 2004; Forster et al., 2008; Watt et al., 2017), offering means by which fronto-striatal circuitry and 5-CSRTT performance can be modulated through stressful episodes (Robbins, 2002).

4.4 | Chronic stress has no impact on sustained attention in ArcAβ mice

In contrast to previous studies with other mouse models of familial AD, and AD patients (Baddeley et al., 2001; Romberg et al., 2011, 2012a,2012b; Sahakian & Coull, 1993), we found that *hAPPswe/arc* overexpression had no impact on adult sustained attention. Importantly, our failure to detect deficits in sustained attention in 15-week-old arcAβ mouse does not reflect a general sparing of cognitive abilities: object recognition memory (C.R. unpublished data) and spatial memory are already severely impaired in arcAβ mice aged 15 weeks, an age when intracellular levels of oligomeric Aβ in the hippocampus and PFC are significantly elevated (Knobloch et al., 2007). Instead, the phenotypic differences between different AD mouse models may relate to genetic variation, such as regional and quantitative difference in the expression of mutant APP. Moreover, individual APP mutations produce specific alterations of post-translational APP processing, leading to a different proportion of APP fragments, with distinct synaptic and cellular effects.

However, despite not having a direct effect on sustained attention, we found that the *hAPParc/swe* genotype prevented the detrimental effect of STR on sustained attention. Importantly, this finding was not causally related to endocrine status because both wt and arcAβ mice responded similarly to an acute stressful challenge. How Aβ oligomers or other aspects of the *hAPParc/swe* genotype modulate the impact of stress is worth investigating in the future, but one possible explanation may be provided by Aβ itself: in its physiological role, Aβ has synaptoprotective effects and is generated in response to excitatory stress, such as after physical impact, ischaemia or chronic stress (Giuffrida et al., 2009; Hefter & Draguhn, 2017; Hick et al., 2015; Kögel, Deller, & Behl, 2012; Palop & Mucke, 2010; Roselli, 2005). Thus, abundant, but not excessive, Aβ oligomers in young arcAβ mice may have protected post-synaptic synapses from overexcitation, and subsequent downregulation, by chronic stress, preventing attentional decline.

However, although intriguing and worth investigating in the future, direct synaptic/neural actions of Aβ oligomers that render these substrates less sensitive to STR are by no means the only potential mechanism explaining the lack of attention deficits in stressed mutant mice. Other factors that might have altered the sensitivity to STR include direct synaptic or neural effects of *hAPP* overexpression, or other physiologically active hAPP cleavage products such as sAPPα and sAPPβ. Furthermore, it is also possible that secondary or compensatory processes activated as a consequence of oligomeric Aβ accumulation and/or transgene expression contribute to the protective effects. For example, Aβ oligomer accumulation and/or APP overexpression are known to cause an inflammatory response (DaRocha-Souto et al., 2011; Heneka et al., 2015), which may have directly changed responsiveness to STR, or may have triggered secondary mechanisms that

reduce sensitivity to further stressors. Specifically, similar to mechanisms discussed in Section 4.2, chronic inflammation (or other aspects of transgene expression) might have epigenetically, genetically or post-translationally interfered with the expression/actions of stress-related peptides. However, it is important to note that the acute stress-induced CORT response remained unaltered in arcAβ mice.

Furthermore, juvenile APP overexpression and/or AD-related *APP/PS1* mutations are known to result in extensive neural network remodelling (Born et al., 2014; Palop et al., 2007; Verret et al., 2012). Characterized by increased network excitability and compensatory inhibitory upregulation, these network alterations in the PFC and hippocampus result in more synchronous neuronal firing and sub-threshold epileptiform discharge. Thus, prefrontal neural networks in arcAβ mice and wild-type mice may simply respond differently to stressful stimuli, or may be differentially sensitive to the detrimental effects of chronic stress, such as synaptic pruning (Arnsten, 2015).

Regardless of the underlying mechanisms, it remains intriguing that an AD-related genotype can protect from the adverse effects of STR.

4.5 | Conclusions

Firstly, our data demonstrate that early life stress in healthy control animals led to a more impulsive and less attentive phenotype in adulthood, which highlights the severe and persistent impact adverse life experience may have on cognitive control. Secondly, we have also shown that an AD-typical increase of Aβ oligomers resulted in increased impulsivity, which suggests that changes to impulse control may, at least in part, be a direct consequence of Aβ-pathology. Because impulsivity increases the vulnerability to other neuropsychiatric disorders, such as depression, schizophrenia and addiction (Bari & Robbins, 2013; Dalley et al., 2008), a better understanding of such non-mnemonic behaviours in AD will be valuable for improving diagnosis and development of new therapeutic strategies for the disease.

Most importantly, however, our findings demonstrated that an AD-predisposing genotype can seemingly neutralize the cognitive effects of chronic stress, which raises new mechanistic questions but also potential preventative and therapeutic strategies. Specifically, modestly elevated Aβ may not necessarily be detrimental to cognitive function, but may also have beneficial effects on cognitive stability.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA ACCESSIBILITY

All data are freely available upon request. Please contact the corresponding author.

AUTHOR CONTRIBUTIONS

A.C. designed the study, acquired and analysed the data, and drafted the manuscript. R.DM. designed paradigms and performed procedures. O.F.X.A. designed the study and revised the manuscript. C.R. designed the study, redrafted and revised the manuscript.

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