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Effect of propranolol on verbal problem solving in autism spectrum disorder

David Q. Beversdorf,[1,2,3] Allen L. Carpenter,[3] Regan F. Miller,[2] Jacquelyne S. Cios,[2] and Ashleigh Hillier[4]

[1]Departments of Radiology, Neurology, and Psychology, and the Thompson Center, University of Missouri, 300 Portland St., Suite 110, Columbia, MO, USA
[2]Department of Neurology, The Ohio State University Medical Center, Columbus, OH 43210, USA
[3]Neuroscience Graduate Studies Program, The Ohio State University, Columbus, OH, USA
[4]Department of Psychology, University of Massachusetts Lowell, Lowell, MA, USA

The noradrenergic system modulates performance on tasks dependent on semantic and associative network flexibility (NF) in individuals without neurodevelopmental diagnoses in experiments using a beta-adrenergic antagonist, propranolol. Some studies suggest drugs decreasing noradrenergic activity are beneficial in ASD. In individuals without neurodevelopmental diagnoses, propranolol is beneficial only for difficult NF-dependent problems. However, in populations with altered noradrenergic regulation, propranolol also benefits performance for simple problems. Due to decreased flexibility of access to networks in ASD, we wished to examine the effect of propranolol on NF in ASD. ASD subjects benefited from propranolol on simple anagrams, whereas control subjects were impaired by propranolol. Further study will be necessary to confirm this finding in a larger sample and to compare clinical response with cognitive response to propranolol.

Keywords: Autism; Asperger syndrome; Noradrenergic; Semantic; Language; Problem solving; Propranolol.

INTRODUCTION

Autism is characterized by impairments in socialization, communication, and the presence of stereotyped and repetitive behaviors with onset before three years of age (American Psychological Association, 1995). Asperger syndrome is characterized by preserved language in the presence of the other characteristics of autism (American Psychological Association, 1995). The term autism spectrum disorder (ASD) is often utilized to collectively describe both syndromes (Beversdorf et al., 1998). A range of theories have been proposed to account for the cognitive impairment in ASD, including inability to utilize context in understanding the environment ('central coherence') (Frith, & Happé, 1994). As a manifestation of decreased utilization of context, research has supported the hypothesis that individuals with ASD have a restriction of flexibility of access to the semantic and associative networks, including decreased semantic clustering in verbal memory (Minshew, & Goldstein, 2001), lack of increased recall of words when syntactic and semantic context is added (Hermelin, & O'Connor, 1970), as well as superior performance on the 'false memory' task (where the semantic and

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Address correspondence to David Q. Beversdorf, MD, Departments of Radiology, Neurology, and Psychology, and the Thompson Center, University of Missouri, 300 Portland St., Suite 110, Columbia, MO 65211, USA. (E-mail: beversdorfd@helath.missouri.edu).

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associative relationships between a heard word list and a not presented lure induce a false memory for the lure in typical individuals) (Beversdorf et al., 2000) despite a more typical performance by the same participants on most other cognitive tests for autism (Beversdorf et al., 1998). Recently, research using functional connectivity fMRI (fcMRI) has demonstrated a potential neural substrate for such decreased network flexibility by showing that the interrelation between active brain regions during sentence comprehension is decreased in ASD (Just, Cherkassky, Keller, & Minshew, 2004). Evidence suggests that individuals with ASD do utilize semantic and associative information to some extent in memory performance, as is demonstrated by other research, including other 'false memory' studies (Bowler, Gardiner, Grice, & Saavalainen, 2000), but not to the same degree as typical subjects. An agent that could affect the semantic and associative networks and other information networks might be of benefit in ASD. Therefore, we wished to examine the effects of pharmacological agents on network flexibility among individuals with ASD.

The anagram task has been utilized in studies investigating the effects of noradrenergic agents on network flexibility in verbal problem solving. In studies assessing anagram performance with propranolol, whereas performance on propranolol was significantly better than on ephedrine or nadolol, it did not significantly differ from placebo (Beversdorf, Hughes, Steinberg, Lewis, & Heilman, 1999; Beversdorf, White, Cheever, Hughes, & Bornstein, 2002). Subsequent research demonstrated that propranolol is beneficial for network flexibility in problem solving particularly when the subject is struggling with the problem (Campbell, Tivarus, Hillier, & Beversdorf, 2008), as would be expected since greater flexibility would be required for such situations where a greater network search is needed, but it can impair performance when subjects are solving problems with ease (Campbell et al., 2008). However, in patients where noradrenergic activity is upregulated, such as in cocaine withdrawal, propranolol benefits performance on the simplest problems (Kelley, Yeager, Pepper, Bornstein, & Beversdorf, 2007). Further research examined the interaction between propranolol and the cognitive effect of stress in individuals without any history of anxiety-related disorders, revealing impairment in anagram performance as well as other tasks involving semantic and associative network flexibility under conditions of stress, which is reversed by propranolol (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007).

Agents that decrease activity of the noradrenergic system are often used for anxiolytic and behavioral purposes in autism. Benefits in language and social behaviors have been reported with beta-adrenergic antagonists (Ratey et al., 1987). Early research suggested increased noradrenergic activity in autism (Martineau, Barthelemy, Jouve, Muh, & Lelord, 1992), but there may be a number of alternative explanations for these findings (Minderaa, Anderson, Volkmar, Akkerhuis, & Cohen, 1994), and pathology is not found in the locus coeruleus in autism (Martchek, Thevarkunnel, Bauman, Blatt, & Kemper, 2006). However, regardless of the ambient activity of the noradrenergic system in autism, the decreased network flexibility in autism might benefit from beta-adrenergic blockade. Therefore, we wished to examine the effect of propranolol on network flexibility in ASD using simpler verbal problem solving tasks with which individuals without neurodevelopmental diagnoses would not be expected to benefit (Campbell et al., 2008). Due to their decreased flexibility of access to networks, we expected that individuals with ASD would have a selective performance benefit from propranolol.

We also gave subjects a memory task as a control task, where we would not expect an effect from propranolol, in order to begin to examine the specificity of this effect on cognitive flexibility in ASD. We selected object memory rather than verbal memory, since effects of propranolol have been observed in certain populations for some aspects of verbal memory (Kelley et al., 2008).

METHODS

Subjects

Eighteen subjects participated in two test sessions, one week apart. Nine of the subjects were high-functioning individuals with ASD (8 males, 1 female) (categorized by the Autism Diagnostic Interview-Revised (Lord, Rutter, & LeCouteur, 1994) for autism and the Gilliam Asperger's Disorder Scale (Gilliam, 2001) for Asperger syndrome) and 9 were age and IQ-matched controls without any neurodevelopmental diagnoses (7 males, 2 females). All subjects had a full scale IQ of at least 85 (high-functioning) and were native English speakers, without other diagnosed language or learning disorders,

and no subjects were taking any noradrenergic agents. All subjects were consented in accordance with the Institutional Review Board at The Ohio State University.

Average subject age (years ± *SD*) was 29.2 ± 9.9 for the ASD subjects, 23.4 ± 2.2 for controls. WAIS-full scale IQ scores (Wechsler, 1997) (score ± *SD*) were 111.1 ± 10.9 (verbal scale = 112 ± 14.4, performance scale = 106.0 ± 12.6) for the ASD subjects, 110.8 ± 5.2 for controls (verbal scale = 115.4 ± 7.6, performance scale = 106.4 ± 8.7).

Procedures

At each test session, participants were given one of two sets of 5-letter anagrams, from our previous work (Beversdorf et al., 1999, 2002), at one session 60 min after taking 40 mg propranolol, and at the other session 60 minutes after taking placebo, in a double-blinded, counterbalanced manner. Heart rate (sampled over 30 s and multiplied by 2) and blood pressure (obtained utilizing a manual blood pressure cuff) were obtained at each session prior to drug administration and again at the time of testing. Each set of anagrams consisted of 14, five-letter anagrams (EXAMPLE: ifrtu → FRUIT). As with previous work (Beversdorf et al., 1999, 2002), a maximum of 120 s was allowed for each problem, with failures recorded as 120 s.

For the control task, subjects were also shown 30 neutral slides at each test session (clocks, turtles, sea shells, etc.) (Lang, Bradley, & Cuthbert, 1997, 2005) for 3 s each, and were subsequently asked to recognize them from a set of distractors.

Analysis

Baseline heart rate and blood pressure were compared between groups using *t*-tests. Heart rate and blood pressure were also compared within subject before and after propranolol as well as placebo using paired *t*-tests.

In our previous work (Beversdorf et al., 1999, 2002), the natural log of solution latencies were calculated (with a minimum of 0 for each anagram). The logarithmic transformation was performed in previous studies because the difference between a 5- and 15-s solution latency was more meaningful for our purposes than the difference between a 105- and 115-s latency. Without this transformation, the results would be largely driven by the results of the more difficult problems (Campbell et al., 2008). However, as this study focused on simpler anagrams, the more difficult problems would not be present. Therefore, in this study, analysis was performed on the natural logarithm of solution latencies, consistent with our previous work, only if the raw scores are not normally distributed. These test session scores were then compared across conditions using a 2 × 2 (drug × group) ANOVA. Subsequent *t*-tests were performed to clarify any effects revealed by this analysis.

RESULTS

Sample characteristics

Average subject age was not significantly different between ASD subjects and controls ($p = .11$). There were no significant differences in WAIS-full scale IQ scores (Wechsler, 1997), or verbal or performance scales between the groups (independent samples *t*-test $p = ns$). No difference was observed for any IQ subtest, except for the digit symbol and digit span subtests, where controls performed better than subjects with ASD (digit symbol = 8.1 ± 2.0 for ASD and 10.8 ± 2.4 for controls, $p < .05$, digit span = 10.5 ± 2.6 for ASD and 13.9 ± 2.7 for controls, $p < .05$).

Hemodynamic response analysis

Heart rate and blood pressure (systolic as well as diastolic) at baseline did not significantly differ between groups. As expected, propranolol resulted in significant decreases between baseline and the time of testing in heart rate as well as blood pressure (systolic blood pressure decreased from 119.2 to 114.7 ($t(17) = 1.99$, $p = .064$), diastolic blood pressure from 77.2 to 75.2 ($t(17) = 2.44$, $p = .027$), heart rate from 74.8 to 68.6 ($t(17) = 2.78$, $p = .013$). No change occurred in blood pressure with placebo, but some decrease in heart rate did occur (heart rate decreased from 76.1 to 72.2 ($t(17) = 2.38$, $p = .030$). To determine whether hemodynamic changes during the placebo condition might have related to habituation to the testing environment, a *post-hoc* comparison was performed to determine whether changes were greatest with placebo in the first test session. For heart rate change, there was no difference between sessions. However, the decrease in systolic blood pressure at the first session was significantly greater than the decrease at the last session ($p = .022$).

Behavioral analysis

Raw anagram latencies were normally distributed (skewness ≤ 1.0 for all conditions), therefore all analysis was performed on raw anagram latencies. On anagram latencies, the 2 × 2 ANOVA revealed a significant interaction effect between drug and group ($F(1, 16) = 4.42$, $p = .05$). All anagrams were used in the analysis, with failed anagrams recorded as 120 s (the maximum allowed time per anagram). There was no main effect for group or drug. To clarify these effects, individual t-tests were performed. Paired t-tests revealed an improvement in anagram latencies (within subject) on propranolol in individuals with ASD ($t(8) = 4.21$, $p = .003$). Furthermore, consistent with the simplest problems in our previous large study on healthy individuals (Campbell et al., 2008), a worse latency performance was revealed (compared within subject) on propranolol for controls ($t(8) = 2.56$, $p = .034$). Independent sample t-tests revealed no significant difference between groups in latency performance in the placebo condition ($t(16) = 1.55$, $p = .16$) (Figure 1, average scores indicated in Table 1). In assessment for the significance of order effects, there was no significant difference within subject for latency performance on the first session as compared to the second session ($t(17) = 1.22$, $p = .24$).

There were no significant effects on the number of problems solved (Table 1), known to be a less sensitive measure than solution latency (Beversdorf et al., 1999, 2002; Campbell et al., 2008). There were also no significant effects on the number of pictures recognized (Table 1).

To begin to examine whether the latency performance effects of propranolol might relate to hemodynamic effects of propranolol, and whether the two groups might differ in this regard, we performed post-hoc analysis determining whether the effects of propranolol on blood pressure and heart rate (blood pressure and heart rate decrease with propranolol – blood pressure and heart rate decrease with placebo) correlated with the effects of propranolol on solution latency (latency with propranolol – latency with placebo). For both the ASD and control groups, there was no significant correlation between propranolol latency performance effects and propranolol hemodynamic effects for systolic or diastolic blood pressure, or heart rate.

DISCUSSION

As expected based on our previous examination of the interaction between task difficulty and the effects of propranolol on network access in verbal problem solving (Campbell et al., 2008), there was an impairment in performance on these simple anagrams with propranolol in individuals without neurodevelopmental diagnoses. However, as indicated by the significant drug by group interaction, the effect of drug on performance in individuals with ASD was significantly different from controls, with ASD subjects performing better with propranolol on the same task. This effect was present despite no significant difference between groups in overall performance on the anagrams.

Norepinephrine is a critical component of the arousal mechanism and has effects on a number of cognitive domains including probabilistic learning and response inhibition, as well as by action on the alpha-1 receptor, extradimensional set-shifting

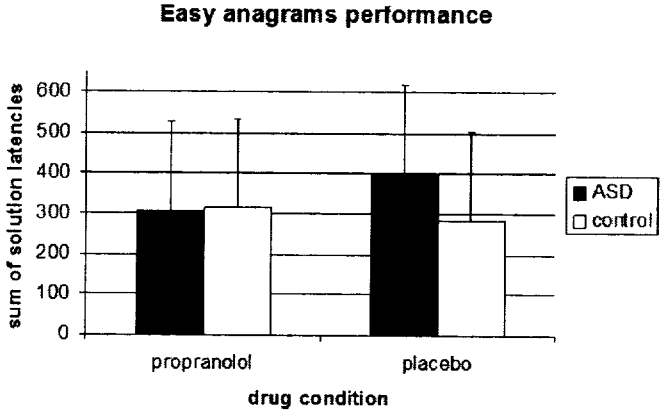

Figure 1. Anagram performance (sum of solution times) for individuals with ASD and individuals without neurodevelopmental diagnoses after administration of propranolol and placebo. Error bars indicate standard deviations.

TABLE 1
Average solution latencies (A), numbers of problems solved (B), and numbers of pictures recognized (out of 30) for each condition with in each group (±*SD*)

	Propranolol	*Placebo*
(A) Average solution latencies (s)		
ASD	22.0 ± 14.0	28.4 ± 17.6
Control	22.5 ± 16.9	20.3 ± 14.4
(B) Number of problems solved		
ASD	12.6 ± 2.0	12.3 ± 2.0
Control	12.8 ± 1.6	13.0 ± 1.1
(C) Number of pictures recognized (out of 30)		
ASD	12.9 ± 6.2	11.6 ± 7.8
Control	13.6 ± 6.0	13.2 ± 8.2

(Robbins, 2007). However, the beta adrenergic receptors in the noradrenergic system appear to modulate the flexibility of access to semantic and associative networks (Alexander et al., 2007).

Previous work has demonstrated that whereas effects of propranolol on the networks in verbal problem solving can be difficult to detect in individuals without neurodevelopmental diagnoses (Beversdorf et al., 1999, 2002; Campbell et al., 2008), a beneficial effect of the drug occurs in the setting of a psychosocial stressor (Alexander et al., 2007) and cocaine withdrawal (Kelley et al., 2007), believed to be due to noradrenergic upregulation, as well as in individuals without such stressors when encountering more difficult problems (Campbell et al., 2008). Whereas it is not certain that norepinephrine is upregulated in autism (Martchek et al., 2006; Martineau et al., 1992; Minderaa et al., 1994) or whether the restriction is more anatomical in nature (Belmonte et al., 2004), our data suggests that the propranolol also has some benefit for performance of the hyper-restrictive networks proposed by network models of autism (Beversdorf, Narayanan, Hillier, & Hughes, 2007; Cohen, 1994; McClelland, 2000). In our study, the two groups did not appear to differ in how hemodynamic responses to propranolol related to cognitive responses to proproanolol. Furthermore, baseline heart rate and blood pressure were similar between groups, offering some suggestion against our finding resulting from a higher baseline stress level in the ASD population. However, assessment of stress regulation in ASD will warrant further investigation using other measures of stress response.

Baseline intelligence as assessed by the WAIS (Wechsler, 1997) was well matched between groups, with no difference in full scale, verbal scale, or performance scale between ASD and controls. However, digit symbol and digit span subtest scores were significantly higher in controls than in ASD. Impairments have previously been reported in digit symbol and digit span performance (Mayes, & Calhoun, 2003; Nakahachi et al., 2006) in ASD. It is difficult to know at this time how this might have affected our results, such as whether propranolol might benefit individuals with ASD since they may struggle more with the verbal problems due to working memory impairment. Future work will be needed in a larger sample of individuals to determine whether performance on a range of attentional and working memory tests affects response to propranolol for verbal problem solving. However, as there was no drug effect on our visual recognition memory task, this does at least suggest that the effects of propranolol in ASD have some specificity to our task. It is unclear, though, as to the relevance of these findings to lower-functioning individuals with ASD.

These findings must be considered as preliminary, due to the small sample size, and should be confirmed in a larger study. Clinical implications cannot be inferred at this time. If confirmed, further research will also need to investigate the range of noradrenergic and anxiolytic agents that have this effect in ASD, the range of other cognitive tasks affected in this manner, the relationship between these findings and stress responses in the testing environment in ASD, and the relationship between these results and the previously reported clinical benefits of such noradrenergic agents in ASD (Ratey et al., 1987).

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