Objective and Background: Autism is characterized by repetitive behaviors and impaired socialization and communication. Preliminary evidence showed possible language benefits in autism from the β-adrenergic antagonist propranolol. Earlier studies in other populations suggested propranolol might benefit performance on tasks involving a search of semantic and associative networks under certain conditions. Therefore, we wished to determine whether this benefit of propranolol includes an effect on semantic fluency in autism.

Methods: A sample of 14 high-functioning adolescent and adult participants with autism and 14 matched controls were given letter and category word fluency tasks on 2 separate testing sessions; 1 test was given 60 minutes after the administration of 40 mg propranolol orally, and 1 test was given after placebo, administered in a double-blinded, counterbalanced manner.

Results: Participants with autism were significantly impaired compared with controls on both fluency tasks. Propranolol significantly improved performance on category fluency, but not letter fluency among autism participants. No drug effect was observed among controls. Expected drug effects on heart rate and blood pressure were observed in both the groups.

Conclusions: Results are consistent with a selective beneficial effect of propranolol on flexibility of access to semantic and associative networks in autism, with no observed effect on phonological networks. Further study will be necessary to understand potential clinical implications of this finding.

Key Words: autism, language, propranolol, noradrenergic, semantic (Cogn Behav Neurol 2011;24:11–17)

Autism is characterized by the presence of communication deficits, impaired social interactions, and repetitive and stereotyped behaviors with onset before 3 years of age. To date, most pharmacotherapeutic interventions have targeted treatment of psychiatric manifestations of autism, such as aggression, anxiety, and obsessive behaviors. Only recently has work begun to explore pharmacotherapeutic interventions aimed at the core cognitive features of autism, with preliminary studies suggesting promise for oxytocin with social behavior and for memantine with language. Development of other potential agents directed at core features of autism would represent a significant advance in treatment.

In our previous work, we examined the effect of noradrenergic agents on language in a variety of settings. Propranolol, a centrally active β-adrenergic antagonist, has long been used for the treatment of test anxiety and performance anxiety. In our initial studies examining the effects of propranolol on verbal problem solving in individuals without neurodevelopmental diagnoses, we found better performance on propranolol than on the noradrenergic agonist ephedrine. We also found better performance on propranolol, a β-adrenergic antagonist that acts centrally and peripherally, compared with nadolol, which acts only in the periphery, suggesting a central mechanism of action. A central mechanism would be predicted based on the effect of norepinephrine on the signal-to-noise ratio of neuronal activity within the cortex, wherein increased signal is proposed to be related to superior performance on attentional tasks, but noise is proposed to represent intrinsic associative activity rather than an absence of coherent input to cortical neurons. However, in neither of our initial studies did the difference between propranolol and placebo reach significance. To better understand how the noradrenergic system affected cognition for these types of tasks, our subsequent research showed that propranolol is beneficial for performance on verbal problem-solving tasks that require a high degree of access to lexical/semantic/associative networks when the individual is struggling with the problem. This would be expected, as greater network access would be required for more difficult tasks requiring a more extensive network search. Benefits were also seen for word fluency tasks, which also involve a search of lexical/semantic/associative networks. Propranolol can impair performance when participants are solving problems with ease. However, in patients with upregulated noradrenergic activity because of exposure to psychosocial stressors or acute cocaine withdrawal, propranolol benefits verbal problem solving regardless of task difficulty. Furthermore, propranolol has also resulted in improved performance.
on naming in patients with anatomical reasons for impaired access to semantic networks, as observed in Broca’s aphasia due to stroke. Therefore, propranolol seems to benefit lexical/semantic/associative network searches through a central mechanism when patients are struggling with problems, but the benefit occurs regardless of task difficulty in situations where increased noradrenergic activity or anatomical changes restrict access to these networks.

Autism is characterized by decreased functional connectivity between distant brain regions in functional magnetic resonance imaging studies during language and other tasks. Consistent with this, network models suggest hyper-restrictive networks in autism. We were interested in exploring the effect of propranolol on aspects of language in autism because of its analogous effects on language in other populations with anatomical impairments in semantic network access, as is observed in Broca’s aphasia. One early, uncontrolled case series has suggested an effect of propranolol on social and language functioning in autism. In our initial pilot study, we found a beneficial effect of propranolol on simple verbal problem solving tasks involving searches through the lexical/semantic network in a small sample of autism patients. However, it remains uncertain whether the effect of propranolol has specificity for semantic networks, or whether it also has effects on phonological networks. It is also unclear whether this effect of propranolol on semantic network access extends beyond the problem-solving domain in autism. Thus, we wished to examine whether propranolol also has an effect on word fluency in autism in a larger sample, and to determine whether the effect differed for semantic and phonological tasks. Therefore, we examined the effect of propranolol on category and letter fluency in autism.

MATERIALS AND METHODS

Participants

A sample of 14 high-functioning adults with autism [10 male, mean age 18.9 ± 2.9 (standard deviation, SD)] as confirmed by the Autism Diagnostic Interview-Revised (ADI-R) and 14 age-matched, sex-matched, and IQ-matched controls [10 male, mean age 19.4 ± 2.0 (SD)] without neuropsychological diagnoses participated in 2 test sessions. All participants had an estimated full scale IQ [Wechsler Abbreviated Scales of Intelligence (WASI)] of at least 80, were native English speakers, and who had no other secondary language or learning disorder by history, and were not taking any noradrenergic agents. Participants with risk factors for exposure to propranolol, such as asthma and depression, were excluded. All participants were consented in accordance with the Institutional Review Board of the University of Missouri.

Drug Administration

At the first test session, participants were randomized to receive either 40 mg propranolol, the dose used in all of our earlier studies, or placebo 60 to 75 minutes before the initiation of testing. At the second test session, participants received the drug not given at the first test session. At least 24 hours separated each test session to allow for complete clearance of the drug. Drug order was counterbalanced with this crossover study such that half of the participants received placebo on the first day and half received propranolol on the first day. Drugs were administered in a double-blinded manner.

Tasks

Heart rate and blood pressure were obtained before drug administration and again at the time of testing. For the letter fluency task, participants were asked to generate as many words as possible that start with a given letter, without giving names and other proper nouns. At the first test session the letters used were “F,” “A,” and “S,” and at the second test session the letters used were “P,” “R,” and “W.” Participants were allowed 30 seconds per letter to generate the words. For the category fluency task, participants were asked to generate as many words as possible that come from a particular category. At the first test session, the categories were “animals,” “things to wear,” and “vegetables,” and at the second test session the categories were “drinks,” “things in the kitchen,” and “hobbies.” Participants were allowed 30 seconds per category to generate the words. In this manner, test version was also counterbalanced across drug condition along with test order. Each of the 2 letter fluency and the 2 category fluency tasks have earlier been shown to be of similar difficulty when administered in the more standard 60 seconds timeframe.

Analysis

The average number of words over 3 trials within each task type (letter, category) was calculated for each test session for each participant. Performance was adjusted for variance because of test order and test version for subsequent analysis. For each task type, a 2 × 2 (group × drug) mixed model analysis of variance was done comparing word fluency between groups and between drug conditions. Post-hoc t tests were then used to define the detected effects, and t tests were also carried out to test our a priori hypothesis, that propranolol would benefit fluency in autism. Blood pressure and heart rate before drug administration and at the time of testing were also compared for each group to confirm the expected hemodynamic effect of the drug using paired t tests.

RESULTS

There was no significant difference in age between groups \(t(27) = 0.602, P = n.s\). In addition, there was no significant difference in IQ between groups [autism WASI IQ = 103.9 ± 12.3 (SD), control WASI IQ = 108.1 ± 7.9 (SD)], \(t(27) = 0.300, P = n.s\]. Among WASI subtests, there was no significant difference between the t-scores for matrix reasoning between groups [autism WASI IQ = 52.6 ± 5.6 (SD), control WASI...
IQ = 50.8 ± 5.9 (SD), \( t(27) = 0.855, P = ns \), but the autism group had slightly lower t-scores for vocabulary [autism WASI IQ = 51.8 ± 10.3 (SD), control WASI IQ = 58.6 ± 6.0 (SD), \( t(27) = 2.12, P = 0.043 \)] (Table 1).

As expected, a significant decrease in heart rate and systolic blood pressure was observed between drug administration and the time of testing with propranolol. Systolic blood pressure decreased from 126.6 ± 13.1 (SD) to 115.4 ± 15.4 (SD) [\( t(27) = 3.06, P = 0.005 \)], and heart rate decreased from 78.1 ± 12.4 to 68.1 ± 9.7 [\( t(27) = 3.69, P = 0.001 \)]. No significant change was observed in heart rate or blood pressure after administration of placebo, and baseline heart rate and blood pressure did not significantly differ between drug conditions. There were no differences in heart rate or blood pressure in either drug condition between groups (control vs autism).

As equal numbers of both groups received drug and placebo for the first test version and the first test session, the raw numbers of words generated for each condition (Table 1) were then adjusted to account for any variability because of test order and test version for subsequent analysis.

A significant main effect of drug was found on the analysis of variance for category fluency [\( F(1,26) = 5.25, P = 0.03 \)] and a trend towards a drug x group interaction effect [\( F(1,26) = 2.86, P = 0.10 \)] was found, with no significant main effect of group (control vs autism) [\( F(1,26) = 2.50, P = 0.13 \)]. There were no main effects or interaction effects on letter fluency.

To address our a priori hypothesis, paired t tests showed a significantly better performance on propranolol than on placebo for the autism group [\( t(13) = 2.12, P = 0.027 \)] for category fluency. Proportional change in performance for each patient in the autism group for the raw total scores on category fluency is indicated in Table 1. Performance on placebo was better for the control group than for the autism group for category fluency [\( t(27) = 2.68, P = 0.019 \)], and there was no difference between groups while on propranolol (Fig. 1). For the letter fluency task, whereas there was also a better performance on placebo for the control group than the autism group [\( t(27) = 2.92, P = 0.012 \)], there was no difference between propranolol and placebo in the autism group (Fig. 2). Drug had no effect on either task among controls.

As the vocabulary score in the autism group was lower than that of the control group, we examined whether proportional change in performance with propranolol related to performance on vocabulary. No correlation was observed between the vocabulary score and effect of propranolol in the autism group (\( r = -0.02, P = ns \)), nor was there a correlation between WASI IQ and effect of propranolol (\( r = 0.10, P = ns \)). Therefore, overall IQ and verbal performance did not relate to the effect of propranolol. However, there was some suggestion of an effect of autism symptomatology, as response to propranolol had a trend toward a correlation with both the Communication (\( r = 0.47, P = 0.089 \)) and Social Interaction (\( r = 0.49, P = 0.076 \)) subscales from the ADI-R, but no relationship was showed with the Repetitive and Stereotyped Behaviors subscale (\( r = 0.11, P = ns \)).

Finally, as evidence has showed use of semantic clustering during phonological fluency, \(^{28}\) we examined whether the proportion of semantically related pairs generated during the phonological fluency task was affected by propranolol. No significant increase in semantically related pairs was observed with propranolol among the autism group [\( t(27) = 0.96, P = ns \)].

**DISCUSSION**

Propranolol, as predicted, has a significant beneficial effect on category fluency in the autism group. The mean improvement in category words generated was 23%, and examination of individual patients shows that 10 of the 14 patients improved with propranolol, and 6 improved their performance by more than 20% (Table 1). There was no effect on performance among controls. Due to the restricted networks in models of autism, \(^{19–22}\) we predicted a more robust effect of propranolol on category fluency in autism than in controls, as has been observed in other patient populations with anatomical causes for impaired network access. \(^{16}\) However, there was no effect of propranolol on letter fluency in the autism group. This initially seems to contrast with our earlier research in other patient populations, where the effect of propranolol seemed to be greater for letter fluency. \(^{13,15}\) In these earlier studies, though, only 1 category was used, whereas 3 letters were used for fluency testing in each condition. Thus, it may be that an insufficient data sample was collected for assessment of drug effects on category fluency compared with letter fluency, contributing to these findings. As tasks involving processing of semantic information seem to use the neocortex in a more distributed manner than tasks involving processing of phonological information, \(^{29}\) one might predict a more robust effect of propranolol on network searches for semantic tasks, such as category fluency, than phonological tasks, such as letter fluency, in a patient population. However, we were unable to detect a significant increase in semantic clustering during the phonological task with propranolol in the autism group, which would have provided further support for an effect on semantic networks.

Further work will be necessary to explore this hypothesis by examining the effect of propranolol on functional connectivity, as connectivity between distant cortical areas is decreased during language tasks in autism. \(^{17}\) Our initial findings suggest that propranolol increases functional connectivity in autism during a phonological categorization task. \(^{30}\) This will need to be examined further using semantic tasks, and while simultaneously monitoring the effects on task performance to better understand how the imaging and behavioral effects are related.

Norepinephrine is a critical component of the arousal mechanism. \(^{31–33}\) The prefrontal cortex, believed
<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>WAIS IQ</th>
<th>Vocabulary (t-scores)</th>
<th>Matrix Reasoning (t-scores)</th>
<th>Placebo Letters</th>
<th>Propranolol Letters</th>
<th>Placebo Category</th>
<th>Propranolol Category</th>
<th>Category Pro/Pla</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>16</td>
<td>110</td>
<td>54</td>
<td>58</td>
<td>20</td>
<td>17</td>
<td>10</td>
<td>27</td>
<td>2.70 ↑↑</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>110</td>
<td>56</td>
<td>56</td>
<td>27</td>
<td>24</td>
<td>24</td>
<td>36</td>
<td>1.50 ↑↑</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>84</td>
<td>38</td>
<td>41</td>
<td>23</td>
<td>24</td>
<td>30</td>
<td>44</td>
<td>1.47 ↑↑</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>113</td>
<td>60</td>
<td>55</td>
<td>28</td>
<td>32</td>
<td>38</td>
<td>53</td>
<td>1.39 ↑↑</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>100</td>
<td>42</td>
<td>59</td>
<td>23</td>
<td>20</td>
<td>18</td>
<td>24</td>
<td>1.33 ↑↑</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>93</td>
<td>41</td>
<td>51</td>
<td>25</td>
<td>23</td>
<td>27</td>
<td>36</td>
<td>1.33 ↑↑</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>127</td>
<td>69</td>
<td>61</td>
<td>28</td>
<td>26</td>
<td>41</td>
<td>48</td>
<td>1.17 ↑↑</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>118</td>
<td>66</td>
<td>55</td>
<td>30</td>
<td>33</td>
<td>40</td>
<td>43</td>
<td>1.08 ↑↑</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>84</td>
<td>34</td>
<td>45</td>
<td>22</td>
<td>19</td>
<td>30</td>
<td>32</td>
<td>1.07 ↑↑</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>104</td>
<td>54</td>
<td>51</td>
<td>31</td>
<td>30</td>
<td>37</td>
<td>39</td>
<td>1.05 ↑↑</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>113</td>
<td>60</td>
<td>55</td>
<td>15</td>
<td>18</td>
<td>40</td>
<td>35</td>
<td>0.88 ↓</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>97</td>
<td>49</td>
<td>48</td>
<td>12</td>
<td>17</td>
<td>28</td>
<td>23</td>
<td>0.82 ↓</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>99</td>
<td>51</td>
<td>49</td>
<td>11</td>
<td>16</td>
<td>28</td>
<td>20</td>
<td>0.71 ↓↓</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>103</td>
<td>51</td>
<td>53</td>
<td>11</td>
<td>15</td>
<td>31</td>
<td>20</td>
<td>0.65 ↓↓</td>
</tr>
<tr>
<td>Mean</td>
<td>18.9</td>
<td>103.9</td>
<td>51.8</td>
<td>52.6</td>
<td>21.9</td>
<td>22.4</td>
<td>30.1</td>
<td>34.3</td>
<td>1.23</td>
</tr>
<tr>
<td>SD</td>
<td>2.9</td>
<td>12.3</td>
<td>10.3</td>
<td>5.6</td>
<td>7.1</td>
<td>6.0</td>
<td>8.9</td>
<td>10.5</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Control

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>WAIS IQ</th>
<th>Vocabulary (t-scores)</th>
<th>Matrix Reasoning (t-scores)</th>
<th>Placebo Letters</th>
<th>Propranolol Letters</th>
<th>Placebo Category</th>
<th>Propranolol Category</th>
<th>Category Pro/Pla</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
<td>116</td>
<td>63</td>
<td>55</td>
<td>19</td>
<td>23</td>
<td>42</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>114</td>
<td>65</td>
<td>51</td>
<td>43</td>
<td>46</td>
<td>32</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>99</td>
<td>55</td>
<td>44</td>
<td>28</td>
<td>24</td>
<td>34</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>114</td>
<td>61</td>
<td>55</td>
<td>26</td>
<td>25</td>
<td>32</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>121</td>
<td>65</td>
<td>59</td>
<td>25</td>
<td>29</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>108</td>
<td>60</td>
<td>49</td>
<td>23</td>
<td>25</td>
<td>30</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>100</td>
<td>60</td>
<td>41</td>
<td>34</td>
<td>28</td>
<td>40</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>115</td>
<td>64</td>
<td>53</td>
<td>33</td>
<td>23</td>
<td>35</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>108</td>
<td>52</td>
<td>49</td>
<td>24</td>
<td>24</td>
<td>33</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>93</td>
<td>43</td>
<td>49</td>
<td>24</td>
<td>22</td>
<td>41</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>99</td>
<td>51</td>
<td>39</td>
<td>31</td>
<td>26</td>
<td>37</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>109</td>
<td>59</td>
<td>51</td>
<td>31</td>
<td>30</td>
<td>40</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>106</td>
<td>54</td>
<td>53</td>
<td>24</td>
<td>27</td>
<td>40</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>111</td>
<td>58</td>
<td>55</td>
<td>28</td>
<td>30</td>
<td>35</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>19.4</td>
<td>108.1</td>
<td>58.6</td>
<td>50.8</td>
<td>28.1</td>
<td>27.3</td>
<td>35.8</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.0</td>
<td>7.9</td>
<td>6.0</td>
<td>5.9</td>
<td>6.0</td>
<td>6.0</td>
<td>4.2</td>
<td>8.9</td>
<td></td>
</tr>
</tbody>
</table>

↑, ↓ indicates direction of change with propranolol; ↑↑, ↓↓ for >20% change.
to be important for various types of cognitive flexibility, has afferent projections to the locus coeruleus in primates, which contains a majority of the noradrenergic neurons in the central nervous system and sends extensive efferents throughout the brain. A range of other cognitive effects have also been described from administration of noradrenergic agents, including effects on motor learning, response inhibition, working memory, and emotional memory.

Our evidence suggests that performance on tasks involving searches through a distributed network (such as the semantic network) to identify appropriate responses (unconstrained flexibility) seems to be affected by the noradrenergic system, whereas other cognitive flexibility tasks such as the Wisconsin Cart Sort Test involves set-shifting between a limited range of options (constrained flexibility), and may not be affected by the noradrenergic system in the same manner. Performance on constrained tasks may even benefit from increased noradrenergic activity, as increased set switching on a 2 alternative forced choice task is associated with increased noradrenergic tone in primate studies.

Constrained flexibility can be further subdivided into intradimensional and extradimensional set-shifting. The dopaminergic system seems to affect intradimensional set-shifting, whereas the noradrenergic system, specifically by action on the α-1 receptor, seems to affect performance on extradimensional set-shifting. The β-adrenergic receptors in the noradrenergic system seem to affect unconstrained flexibility, which would seem to be the aspect of cognitive flexibility most involved in word fluency.

Another possibility is that the current finding of an effect of propranolol in the autism group alone is because of altered noradrenergic activity in autism. Early research showed findings suggestive of increased noradrenergic activity in autism, including increased plasma epinephrine and norepineprine, and altered urinary excretion of various catecholaminergic metabolites. The increased activity in these studies, though, may have related to the reaction among individuals with autism to obtaining blood or urine samples, rather than because of autism itself. In addition, there is no atypical cell count, cell density, or change in volume of the locus coeruleus in autism. However, because of the interesting observation of improved behavior during febrile episodes in autism, recent theories have proposed that a developmentally dysregulated noradrenergic system may be a significant component in autism.

Regardless of whether the noradrenergic system is directly affected in autism, or whether the specific finding of a cognitive effect in autism is because of the altered connectivity in autism, the findings do suggest an effect of propranolol with some specificity to semantic and associative networks in contrast to phonological networks in autism, and that this effect extends beyond the problem-solving domain. It will be important to determine the range of the effects of propranolol on other networks in autism, as well as further assessment of word fluency using the standard 60 seconds for each stimulus. The shorter timeframe was used in this study to allow a range of other unrelated tasks to be completed during the peak level of propranolol. Future studies will also need to determine whether sustained doses will have the same effects. Furthermore, it will be important to determine which individuals with autism are most likely to show an effect from propranolol among the autism population. For example, most of the patients in the study reporting improved behavior during febrile illnesses, upon which the hypothesis of dysregulated noradrenergic development was based, were lower functioning individuals. It will be important to determine whether individuals with autism differ in their response to propranolol based on their phenotypic presentation or range of symptomatology. The individuals with autism in this study did have lower performance on vocabulary, but we were unable to detect a relationship between vocabulary or WAIS IQ and response to propranolol. However, it should be noted
that all of our patients were higher functioning; therefore, the effect on lower functioning individuals remains unknown. The trend toward a correlation between drug response and the ADI-R Communication and Social Interaction subscales, which indicates the degree of impairment in these areas during development, is intriguing, and warrants further investigation in a larger sample to determine whether response to propranolol is greater in more affected individuals. Clinical implications cannot be drawn from this examination of the effect of single doses of propranolol on aspects of the cognitive network. Clinical trials would be necessary for that purpose.

REFERENCES

43. Lapiz MDS, Morilak DA. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured
44. Lake CR, Ziegler MG, Murphy DL. Increased norepinephrine levels and decreased dopamine-beta-hydroxylase activity in primary autism. *Arch Gen Psychiatry.* 1977;34:553–556.