Supplementary materials

Self-injurious behavior exploratory analysis

As altered pain experience may contribute to self-injurious behaviors (SIBs) in ASD, we explored differences in NPS and modulatory regions related to presence of SIB within the ASD group, as measured by the RBS-R. RBS-R data was available for 12 of the individuals in the ASD group, eight of which endorsed some form of SIB. **Figure S1** depicts response time courses during pain stimulation by group, with the ASD group separated by presence or absence of SIBs (ASD+SIB, n=8; ASD-SIB, n=4). Importantly, there were no differences in IQ, pain rating, or heat pain thresholds between SIB subgroups.

As the BOLD signal response was similar across the NPS, **Figure S1A** illustrates the pattern we observed across the NPS, using a representative NPS region (left insula) for illustration. In the NPS, the ASD+SIB group shows early phase increases and sustained intermediate/late phase decreases in BOLD signal compared to the TC group that are absent in the ASD-SIB group, suggesting that the effect seen in the NPS may be driven by the subgroup of individuals with ASD and SIB. Figure S1B-D illustrates patterns in the putative modulators of NPS. In the left PCC (**Figure S1B**), the ASD+SIB group shows decreased BOLD signal compared to the TC group in the intermediate/late phases, similar to the pattern observed in the NPS. In the left dlPFC (**Figure S1C**), the ASD+SIB group shows decreased signal relative to the TC group that is limited to a single timepoint within the intermediate phase. In the left sgPFC (**Figure S1D**), the ASD+SIB group shows decreased signal in sgPFC relative to the TC group during the early and intermediate phases. In contrast, the ASD-SIB group shows *increased* signal relative to the TC group during all three phases, and relative to the ASD+SIB during the intermediate phase. All comparisons in Figure 5 are $p<0.05$, uncorrected.

Because our sample was small and comprised of high-functioning adults with a limited range of SIB assessed with a parent-report instrument adapted for self-report (Bodfish et al., 2000), these results should be considered exploratory in nature and interpreted cautiously. However, we noted that the late reduction of BOLD response both within the NPS and in the default mode network was driven by the subset of the ASD group that exhibited SIB. We do not interpret these

findings as an overall hyporeactivity to pain in individuals with ASD and SIB, given the intact early response in the NPS (see Figures 2, S1a), and the deactivation of the sgPFC (Figure S1d), which would be consistent with increased pain perception via decreased antinociceptive input in individuals with SIB. Rather, our results indicate that only the neural response to *sustained* painful experience is more heavily attenuated in the subgroup of individuals with ASD and associated SIB, suggesting altered affective or cognitive evaluation of sustained pain (Shackman et al., 2011). It is plausible that this shutdown of the expected response to sustained pain enables prolonged or repeated bouts of SIB in these individuals, and that the perpetuation of their SIB is mechanistically distinguishable from its initiation, which may be more related to higher-order compulsive traits (Muehlmann and Lewis, 2012).

The forms of SIB most commonly endorsed in our sample (scratching, skin picking) are considered diagnostically to have a strong overlap with obsessive compulsive spectrum disorders (Stein et al., 2010). This suggests it may be useful to examine this population as an additional comparison group in future studies, as well as designs that allow comparison of initiation and maintenance of SIB. However, the aforementioned limitations of this study preclude any definitive conclusions about SIB. Rather, we view this preliminary result as hint that may help inform future studies of pain perception in individuals with autism and SIB. If replicated, our findings may help to clarify discrepant results from experimental studies using discrete, acute painful stimuli compared to sustained pain stimuli that are likely a more ecologically valid representation of the prolonged or repetitive bouts of painful self-stimulation characteristic of SIB in ASD.

References

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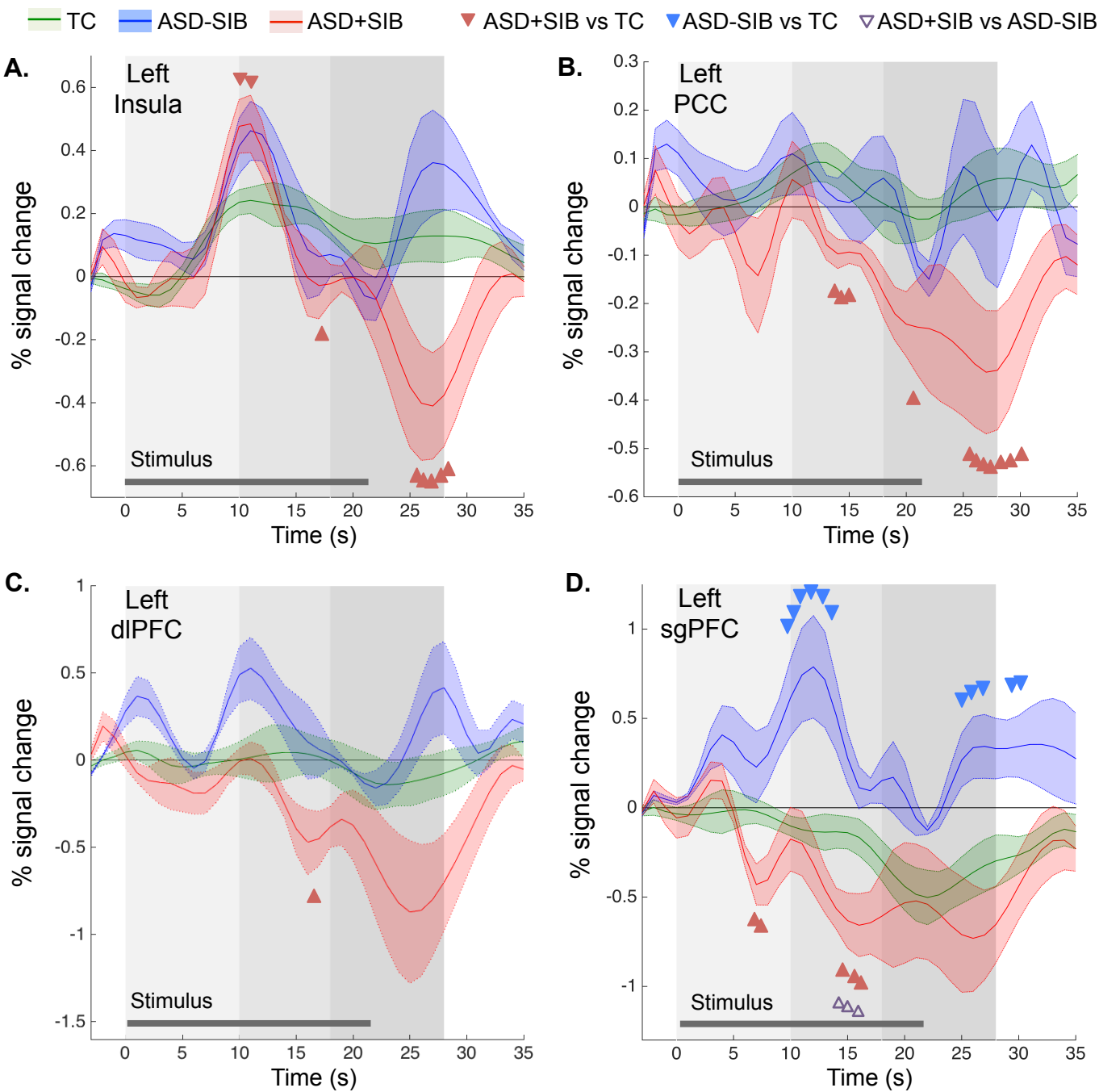
Figure S1. Region of interest analysis: Time courses of the hemodynamic response within the typical comparison (TC) group, and ASD with (ASD+SIB) and without (ASD-SIB) self-injurious behaviors. (A) Representative time course from the neural pain signature (NPS, left insula) where similar response patterns exist across regions. (B-D) Time courses of modulatory regions outside of the NPS. Gray shading indicates phase of pain stimulation (early, light to late, dark). Triangles indicate time-points with significant comparisons between groups corresponding to legend ($p<0.05$, uncorrected). PCC, posterior cingulate cortex; sgPFC, subgenual prefrontal cortex; dlPFC, dorsolateral prefrontal cortex.


TC
ASD-SIB
ASD+SIB
ASD+SIB vs TC
ASD-SIB vs TC
ASD+SIB vs ASD-SIB
A.
Left Insula
% signal change
Stimulus
Time (s)
B.
Left PCC
% signal change
Stimulus
Time (s)
C.
Left dlPFC
% signal change
Stimulus
Time (s)
D.
Left sgPFC
% signal change
Stimulus
Time (s)